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(54) Title: HUMAN BREAST AND OVARIAN CANCER ASSOCIATED GENE SEQUENCES AND POLYPEPTIDES (57) Abstract <p>This invention relates to newly identified breast, ovarian, breast cancer and/or ovarian cancer related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "breast/ovarian cancer antigens", and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such breast/ovarian cancer antigens for detection, prevention and treatment of disorders of the female reproductive system, particularly disorders of the breast and/or ovary, including the presence of breast cancer and/or ovarian cancer. This invention relates to the breast/ovarian cancer antigens as well as vectors, host cells, antibodies directed to breast/ovarian cancer antigens and recombinant and synthetic methods for producing the same. Also provided are diagnostic methods for diagnosing and treating, preventing and/or prognosing disorders related to the female reproductive system, particularly disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention.</p>		

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Human Breast and Ovarian Cancer Associated Gene Sequences and Polypeptides

5 *Field of the Invention*

This invention relates to newly identified breast, ovarian, breast cancer, and ovarian cancer related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "breast/ovarian cancer antigens," and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such
10 breast/ovarian cancer antigens for detection, prevention and treatment of disorders of the female reproductive system, specifically disorders of the breast or ovary, particularly the presence of breast and/or ovarian cancer. This invention relates to the breast/ovarian cancer antigens as well as vectors, host cells, antibodies directed to breast/ovarian cancer antigens and recombinant and synthetic methods for producing the same. Also provided are
15 diagnostic methods for diagnosing and treating, preventing and/or prognosing disorders related to the female reproductive system, specifically disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention. The present invention further
20 relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention.

Background of the Invention

Breast cancer represents the most frequent cause of early morbidity and mortality in
25 women in North America (Harris et al, New Eng. J. Med. 327:319, 390 and 473 (1992)). It is generally believed that this malignancy arises from a multi step process involving mutations in a relatively small number of genes, perhaps 10 or less. These mutations result in significant changes in the growth and differentiation of breast tissue that allow it to grow independent of normal cellular controls, to metastasize, and to escape immune surveillance. The genetic
30 heterogeneity of most breast cancers suggests that they arise by a variety of initiating events

and that the characteristics of individual cancers are due to the collective pattern of genetic changes that accumulate (Harris et al. *New Eng. J. Med.* 327:319, 390 and 473 (1992)).

The classes of genes that are involved in breast cancer are not unlike those found in a number of other well characterized malignancies, although some are highly specific for breast cancer. In particular, mutations in the genes that encode receptors involved in binding to estrogen and progesterone are particularly important because they likely cause the breast cells to proliferate while rendering them unresponsive to the antitumor effects of these hormones in advanced malignancy. In addition, changes in the genes that encode growth factors, other receptors, signal transduction molecules, and transcription factor molecules are frequently involved and have alterations that are involved in the development and progression of breast cancer (King, *Nature Genetics* 2:125 (1992)). The characterization of the type and number of mutations seen in individual breast cancers is useful in classifying the biological properties of individual cancers and in determining the prognosis for individual patients. For example, the *erbB2/HER2/neu* gene is particularly valuable in predicting the prognosis of both node-positive and node-negative patients based on the amplification status of the gene (King, *Science* 250:1684 (1990)). Several additional members of this family have been discovered but the ligand for *erbB2/HER2/neu* remains unknown. It is anticipated that further advances in therapeutics will be achieved by the development of therapies that disrupt aberrant growth signaling pathways or affect the cellular interactions of breast cancer cells with native stroma or metastatic sites.

Although oncogenes are likely to be very important in breast cancer, tumor suppressor genes may also play an important role. Certain of these genes, including p53 and Rb-1, are essential to the normal mechanisms that control cell cycle events, especially those checkpoints at the border of the different stages of the cell cycle (Hollstein et al, *Science* 253:49 (1991); Srivastava et al, *Nature* 348:747 (1990)).

In 1969, Li and Fraumeni documented a familial cancer syndrome that had an autosomal dominant pattern of expression (Li et al, *Ann. Intern. Med.* 71:747 (1969)). Members of these families had sarcomas, breast cancers, brain tumors, leukemias, adrenocortical carcinomas, and other malignancies. Family studies demonstrated that the gene responsible for the syndrome was located on chromosome 17, and examination of the p53 gene as a candidate gene revealed that this gene was mutated in five families (Malsin et al, *Science* 250:1233 (1990)). In the last two years, two genes linked to familial breast cancer,

designated BRCA1 and BRCA2, have been isolated and characterized. BRCA1 is at 17q21 (Claus et al, Am. J. Epidemiology 131:961 (1990); Hall et al, Science 250:1684 (1990); Easton et al, Am. J. of Human Genetics 52 (4):678 (1993); Black et al, Am. J. of Human Genetics 52 (4):702 (1993); Bowcock et al, Am. J. of Human Genetics 52 (4):718 (1993); Miki et al, Science 266:66 (1995)). The demonstration of loss of heterozygosity (LOH) at 17q25 has defined another potential tumor suppressor gene (Lindblom et al, Human Genetics 91:6 (1993); Cornelis et al, Oncogene 8:781 (1993); Theile et al, Oncogene 10:439 (1995)).

There is a need, therefore, for identification and characterization of such factors that modulate activation and differentiation of breast and ovarian cells, both normally and in disease states. In particular, there is a need to isolate and characterize additional molecules that mediate apoptosis, DNA repair, tumor-mediated angiogenesis, genetic imprinting, immune responses to tumors and tumor antigens and, among other things, that can play a role in detecting, preventing, ameliorating or correcting dysfunctions or diseases.

The present invention relates at least in part, to a novel breast and ovarian and breast and ovarian cancer related polynucleotides and polypeptides. The discovery of these breast and ovarian cancer related polynucleotides provides new compositions which are useful in the diagnosis, prevention and treatment of disorders of the female reproductive system, particularly of the ovary including, but not limited to ovarian cancer, and the breast, including but not limited to breast cancer.

Summary of the Invention

The present invention includes isolated nucleic acid molecules comprising, or alternatively, consisting of, a breast, ovarian, breast cancer and/or ovarian cancer associated polynucleotide sequence disclosed in the sequence listing (as SEQ ID Nos:1 to 418) and/or contained in a human cDNA clone described in Tables 1, 2 and 5 and deposited with the American Type Culture Collection ("ATCC"). Fragments, variant, and derivatives of these nucleic acid molecules are also encompassed by the invention. The present invention also includes isolated nucleic acid molecules comprising, or alternatively consisting of, a polynucleotide encoding a breast, ovarian, breast cancer, and/or ovarian cancer polypeptide. The present invention further includes breast, ovarian, breast cancer, and/or ovarian cancer polypeptides encoded by these polynucleotides. Further provided for are amino acid

sequences comprising, or alternatively consisting of, breast, ovarian, breast cancer, and/or ovarian cancer polypeptides as disclosed in the sequence listing (as SEQ ID Nos: 419 to 836) and/or encoded by a human cDNA clone described in Tables 1, 2 and 5 and deposited with the ATCC. Antibodies that bind these polypeptides are also encompassed by the invention.

5 Polypeptide fragments, variants, and derivatives of these amino acid sequences are also encompassed by the invention, as are polynucleotides encoding these polypeptides and antibodies that bind these polypeptides. Also provided are diagnostic methods for diagnosing and treating, preventing, and/or prognosing disorders related to the female reproductive system, specifically disorders related to the breast and/or ovary, including breast cancer
10 and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention.

Detailed Description

15

Tables

Table 1 summarizes some of the breast/ovarian cancer antigens encompassed by the invention (including contig sequences (SEQ ID NO:X) and the cDNA clone related to the contig sequence) and further summarizes certain characteristics of the breast/ovarian cancer
20 polynucleotides and the polypeptides encoded thereby. The first column shows the "SEQ ID NO:" for each of the 418 breast/ovarian cancer antigen polynucleotide sequences of the invention. The second column provides a unique "Sequence/Contig ID" identification for each breast, ovarian, breast cancer and/or ovarian cancer associated sequence. The third column, "Gene Name," and the fourth column, "Overlap," provide a putative identification
25 of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database and the database accession no. for the database sequence having similarity, respectively. The fifth and sixth columns provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as
30 SEQ ID NO:Y. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity), respectively, observed between the aligned sequence

segments of the translation product of SEQ ID NO:X and the database sequence. The ninth column provides a unique "Clone ID" for a cDNA clone related to each contig sequence.

Table 2 summarizes ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application.

Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, fifteen or more of any one or more of these public EST sequences are optionally excluded from certain embodiments of the invention.

Table 4 lists residues comprising antigenic epitopes of antigenic epitope-bearing fragments present in most of the breast, ovarian, breast cancer or ovarian cancer associated polynucleotides described in Table 1 as predicted by the inventors using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power Macintosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). Breast, ovarian, breast cancer and/or ovarian cancer associated polypeptides (e.g., SEQ ID NO:Y, polypeptides encoded by SEQ ID NO:X, or polypeptides encoded by the cDNA in the referenced cDNA clone) may possess one or more antigenic epitopes comprising residues described in Table 4. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. The residues and locations shown in column two of Table 4 correspond to the amino acid sequences for most breast, ovarian, breast cancer and/or ovarian cancer associated polypeptide sequence shown in the Sequence Listing.

Table 5 shows the cDNA libraries sequenced, and ATCC designation numbers and vector information relating to these cDNA libraries.

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be

"isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X (as described in column 1 of Table 1) or the related cDNA clone (as described in column 9 of Table 1 and contained within a library deposited with the ATCC). For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown in column 9 of Table 1, each clone is identified by a cDNA Clone ID. Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. In addition to the individual cDNA clone deposits, most of the cDNA libraries from which the clones were derived were deposited at the American Type Culture Collection (hereinafter "ATCC"). Table 5 provides a list of the deposited cDNA libraries. One can use the Clone ID to determine the library source by reference to Tables 2 and 5. Table 5 lists the deposited cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone ("Clone ID") isolated from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1 correlates the Clone ID names with SEQ ID NOs. Thus, starting with a SEQ ID NO, one can use Tables 1, 2 and 5 to determine the corresponding Clone ID, from which library it came and in which ATCC deposit the library is contained. Furthermore,

it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), and/or sequences contained in the related cDNA clone within a library deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also included within "polynucleotides" of the present invention are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA⁺ sequences (such as any 3' terminal polyA⁺ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

The polynucleotides of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

"SEQ ID NO:X" refers to a breast/ovarian cancer antigen polynucleotide sequence described in Table 1. SEQ ID NO:X is identified by an integer specified in column 1 of Table 1. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF)

encoded by polynucleotide SEQ ID NO:X. There are 418 breast/ovarian cancer antigen polynucleotide sequences described in Table 1 and shown in the sequence listing (SEQ ID NO:1 through SEQ ID NO:418). Likewise there are 418 polypeptide sequences shown in the sequence listing, one polypeptide sequence for each of the polynucleotide sequences (SEQ ID NO:419 through SEQ ID NO:836). The polynucleotide sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, a polypeptide sequence corresponding to polynucleotide sequence SEQ ID NO:1 is the first polypeptide sequence shown in the sequence listing. The second polypeptide sequence corresponds to the polynucleotide sequence shown as SEQ ID NO:2, and so on. In other words, since there are 418 polynucleotide sequences, for any polynucleotide sequence SEQ ID NO:X, a corresponding polypeptide SEQ ID NO:Y can be determined by the formula $X + 418 = Y$. In addition, any of the unique "Sequence/Contig ID" defined in column 2 of Table 1, can be linked to the corresponding polypeptide SEQ ID NO:Y by reference to Table 4.

The polypeptides of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation,

hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

The breast, ovarian, breast cancer and/or ovarian cancer polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The breast, ovarian, breast cancer and/or ovarian cancer polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to

a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

"A polypeptide having functional activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular assay, such as, for example, a biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

The functional activity of the breast/ovarian cancer antigen polypeptides, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an antibody to the full length polypeptide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See

generally, Phizicky, E., et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, physiological correlates polypeptide of the present invention binding to its substrates (signal transduction) can be assayed.

5 In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants derivatives and analogs thereof to elicit polypeptide related biological activity (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

10

Breast, Ovarian, Breast Cancer and Ovarian Cancer Associated Polynucleotides and Polypeptides of the Invention

15 It has been discovered herein that the polynucleotides described in Table 1 are expressed at significantly enhanced levels in human breast, ovarian, breast cancer and/or ovarian cancer tissues. Accordingly, such polynucleotides, polypeptides encoded by such polynucleotides, and antibodies specific for such polypeptides find use in the prediction, diagnosis, prevention and treatment of disorders related to the female reproductive system, specifically disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer as more fully described below.

20 Table 1 summarizes some of the polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and the related cDNA clones) and further summarizes certain characteristics of these breast, ovarian, breast cancer and/or ovarian cancer associated polynucleotides and the polypeptides encoded thereby.

Table 1

Seq ID No.	Sequence/ Contig ID	Gene Name	Overlap	HGS Nucleotide		% Identity	% Similarity	Clone ID
1	419266	monoamine oxidase B [Homo sapiens] >gij187376 monoamine oxidase B [Homo sapiens] >bbs1134021 monoamine oxidase B, MAO B [human, platelet, Peptide Partial, 520 aa] [Homo sapiens] >pirJH0817JH0817 amine oxidase (flavin-containing) (EC 1.4.3.4) B - human >	gij187359	Start	End	95	95	HAGFP75
2	429114			51	383			HATDC43
3	506777			51	233			HRGCY74
4	508678	(AF059293) cytokine-like factor-1 precursor [Homo sapiens] >spO75462O75462 CYTOKINE-LIKE FACTOR-1 PRECURSOR. Length = 422	gij3372627	3	155	100	100	HFJUG81
5	508968	DNA helicase [Homo sapiens] >pirA58836A55311 DNA helicase RECQL - human Length = 659	gij619863	2	739	95	96	HHTLH91
6	509029			770	1096			HLMDG72
7	519726			359	529			HCSSB83

8	522632		3	299		HRGBG45
9	524655		522	686		HUSGS36
10	525847	glyoxalase II [Homo sapiens] >sp Q16775 GLO2_HUMAN HYDROXYACYLGLUTATHIONE HYDROLASE (EC 3.1.2.6) (GLYOXALASE II) (GLX II). Length = 260	1	162	54	73 H6EDP14
11	530306		239	355		HCHCC28
12	532818	(AF035178) elongation factor 1 A2 [Oryctolagus cuniculus] >gi 38456 elongation factor 1 alpha-2 [Homo sapiens] >pir S35033 EFHUA2 translation elongation factor eEF-1 alpha-2 chain - human >sp Q05639 EF12_HUMAN ELONGATION FACTOR 1-ALPHA 2 (EF-1-ALPHA-2) (S	43	441	95	95 HAMFD92
13	533385		1258	1827		HTWAO42
14	533532	actin capping protein alpha subunit [Homo sapiens] >gi 2393732 (AC002543) f-actin capping protein alpha-2 subunit [Homo sapiens] >sp P47755 CAZ2_HUMAN F- ACTIN CAPPING PROTEIN ALPHA-2 SUBUNIT (CAPZ). >gi 433308 capping protein alpha [Homo sapiens] {SUB 3-2	18	947	95	95 HETCD42

15	534852	(AF041472) ataxin-2 [Mus musculus] >sp O70305 O70305 SPINOCEREBELLAR ATAXIA 2 HOMOLOG (ATAXIN-2). Length = 1285 R kappa B [Homo sapiens] >pir S52863 S52863 DNA-binding protein R kappa B - human >sp Q15312 Q15312 R KAPPA B. Length = 1324	gil3005020	3	869	77	77	HCE4Q55
16	537910		gil695579	3	443	100	100	HTOAO52
17	538460			574	1026			HSSMY42
18	539577	transcriptional activator [Homo sapiens] >gnl PID d1005685 HSNF2b [Homo sapiens] >pir S45252 S45252 SNF2beta protein - human >gil4056413 (AC006127) SN24_HUMAN; nuclear protein GRB1; homeotic gene regulator; SNF2-BETA [Homo sapiens] {SUB 814-1474} Length =	gil902046	1	540	89	89	HKADQ93
19	548379	complement protein C7 precursor [Homo sapiens] >pir A27340 A27340 complement C7 precursor - human >sp P10643 CO7_HUMAN COMPLEMENT COMPONENT C7 PRECURSOR. Length = 843 proteasome subunit HsN3 [Homo sapiens] >pir S50147 S50147 multicatalytic endopeptidase complex (EC 3.4.99.46) beta chain N3 - human >sp P28070 PRCB_HUMAN PROTEASOME BETA CHAIN PRECURSOR (EC 3.4.99.46) (MACROPAIN BETA CHAIN)	gil179716	92	1336	92	92	HATCK25
20	548489		gnl PID d100 6192	3	857	99	99	HCGAF33

(MULTICATALYTIC ENDOPEPTIDASE
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21	548595	inosine monophosphate dehydrogenase type II [Homo sapiens] >gi 1702964 inosine monophosphate dehydrogenase type II [Homo sapiens] >pir 52303 A31997 IMP dehydrogenase (EC 1.1.1.205) II - human >sp P12268 IMD2_HUMAN INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE	gi 602458	971	1525	100	100	HTXEE92
22	549337	stromelysin-3 precursor [Homo sapiens] Length = 488	gi 456257	449	1081	96	96	HJMAF23
23	549777			54	293			HPMAC61
24	553091	pancreatic peptidylglycine alpha-amidating monooxygenase, PAM=membrane-bound isoform {alternatively spliced, clone PAM-3, transmembrane domain (Ba region)} [human, islet cell tumor cell line QGP-1, Peptide Partial, 971 aa] [Homo sapiens] >sp Q16252 Q16252	bbs 159681	898	2598	97	97	HEMFU73
25	553827	B-CAM gene product [Homo sapiens] >pir 37202 37202 B-CAM protein - human Length = 588	gi 535179	2	388	80	80	HIBHMI67

26	556350		263	655			HCHOC59	
27	556351	'FKBP52; 52 kD FK506 binding protein' [Homo sapiens] >pir A46372 A46372 immunophilin FKBP52 - human >sp Q02790 FKB4_HUMAN P59 PROTEIN (HSP BINDING IMMUNOPHILIN) (HBI) (POSSIBLE PEPTIDYL-PROLYL CIS-TRANS ISOMERASE) (EC 5.2.1.8) (PPIASE) (ROTAMASE) (FKBP5 ubiquitin conjugating enzyme [Homo sapiens] >pir A49630 A49630 ubiquitin conjugating enzyme - human (fragment) Length = 298 (AD001530) putative [Homo sapiens] >sp G2335055 G2335055 XAP-5. >gnl PID d1012538 HXC-26 [Homo sapiens] {SUB 15-339} >gij 203974 XAP-5 gene product [Homo sapiens] {SUB 66-339} Length = 339 adipocyte lipid-binding protein [Homo sapiens] >pir A33363 FZHU fatty acid-binding protein, adipocyte - human >sp P15090 FABA_HUMAN FATTY ACID-BINDING PROTEIN, ADIPOCYTE (AFABP) (ADIPOCYTE LIPID-BINDING PROTEIN) (ALBP) (A-FABP). {SUB 2-132} Length = 132 N-cadherin [Homo sapiens] Length = 747	gij 186390	2	1216	97	HE8DF57	
28	557007		gij 388309	3	698	99	100	HTEJK85
29	558140		gij 2335055	3	1070	71	71	HKAAM18
30	558456		gij 178347	69	332	100	100	HISBQ67
31	558708		gij 416293	3	515	79	79	HSYBX61
32	574789			301	402			HLDNM79

33	578203		2	445		H6EDN57
34	585385	precursor polypeptide (AA -21 to 782) [Homo sapiens] >pir A35954 A35954 endoplasmic precursor - human >sp P14625 ENPL_HUMAN ENDOPLASMIN PRECURSOR (94 KD GLUCOSE-REGULATED PROTEIN) (GRP94) (GP96 HOMOLOG) (TUMOR REJECTION ANTIGEN 1). Length = 803 leukocyte adhesion glycoprotein precursor [Homo sapiens] Length = 1152	99	347	71	IIQI:MI70
35	588869		1	720	98	HDPFK39
36	597076	preferentially expressed antigen of melanoma [Homo sapiens] >sp P78395 P78395 PREFERENTIALLY EXPRESSED ANTIGEN OF MELANOMA. Length = 509 sigma receptor [Homo sapiens] >gil 916800 SR31747 binding protein 1 [Homo sapiens] >gil 2914740 (AF001977) type I sigma receptor [Homo sapiens] >pir JC5266 JC5266 sigma receptor 1 - human >sp Q99720 Q99720 SIGMA RECEPTOR. Length = 223	80	811	77	HEETHIE66
37	598656		3	587	100	HMEIY05

38	611880	Acetyl-CoA:acetyltransferase (EC 2.3.1.9) (Acetoacetyl-CoA thiolase). [Escherichia coli] >gil1788554 (AE000311) acetyl-CoA acetyltransferase [Escherichia coli] >pir F64992 F64992 hypothetical protein b2224 - Escherichia coli (strain K-12) >sp P76461 ATOB_	gn PID d1016745	1	108	100	100	HOVAS88
39	614329	ORF, HEIR-1; pot. neuroblastoma-associated regulator [Homo sapiens] >gil395338 helix-loop-helix protein [Homo sapiens] >gil512437 HEIR-1 [Homo sapiens] {SUB 30-148} Length = 148	gil490013	300	755	86	86	HFPCCQ2
40	616066			121	213			HSIGC05
41	620956	ribosomal protein S9 [Rattus norvegicus] >pir JN0587 S21497 ribosomal protein S9 - rat Length = 194	gil57143	3	473	95	97	HOFOB28
42	621889	unnamed protein product [unidentified] >gil468550 CCT (chaperonin containing TCP-1) epsilon subunit [Mus musculus] >pir S43061 S43061 t-complex-type molecular chaperone Ccte - mouse Length = 541	gn PID c306129	16	423	95	97	HOFOC44
43	624017	(AB003732) polyubiquitin [Cricetulus griseus] >sp O35080 O35080 POLYUBIQUITIN. >gil4105408 (AF045474) polyubiquitin [Schistosoma mansoni] {SUB 694-988} Length = 1038	gil2627133	1	1170	95	97	HMCBS12

44	651784	histone H2A.X [Homo sapiens] >pir S07631 S07631 histone H2A.X - human >sp P16104 H2AX_HUMAN HISTONE H2A.X. {SUB 2-143} Length = 143	gi 31973	2	514	98	98	HKGA194
45	651826	keratin, 55K type II cytoskeletal - human (fragment) Length = 489	pir B24177 B 24177	2	1300	86	86	HNTAH42
46	653282	phosphate transfer protein B precursor, mitochondrial - bovine Length = 361	pir D53737 D 53737	30	392	90	90	HOFNY90
47	657122			1	204			HKGAQ13
48	661442	rab1B protein (AA 1 - 201) [Rattus sp.] Length = 201	gi 57006	1	672	98	99	HICHMI33
49	664914	phosphotyrosyl phosphatase activator [Oryctolagus cuniculus] >pir B54021 B54021 phosphotyrosyl phosphatase activator PTPA - rabbit >sp Q28717 Q28717 PHOSPHOTYROSYL PHOSPHATASE ACTIVATOR. Length = 323	gi 509144	1	228	98	100	HEGAK11
50	666654			63	395			HOFNL37
51	667084	cytokeratin 17 [Homo sapiens] >gi 34075 keratin related product [Homo sapiens] >pir S30433 S30433 keratin 17, cytoskeletal - human >sp Q04695 K1CQ_HUMAN KERATIN, TYPE I CYTOSKELETAL 17 (CYTOKERATIN 17) (K17) (CK 17) (39.1) (VERSION 1). {SUB 2-432} Length	gi 30379	3	1379	100	100	HKADA74

52	667380	cell surface glycoprotein [Homo sapiens] >gnl PID d1006754 TALLA-1 [Homo sapiens] >gnl PID d1001976 cell surface glycoprotein [Homo sapiens] >pir 39368 39368 T-cell acute lymphoblastic leukemia associated antigen 1 - human >sp P41732 A15_HUMAN CELL SURF	gnl PID d1001976	1	474	100	100	HMIBK53
53	669530			264	440			HPFCJ30
54	671315	cell cycle checkpoint control protein [Homo sapiens] >sp Q99638 Q99638 CELL CYCLE CHECKPOINT CONTROL PROTEIN. Length = 391	gij 765956	320	1279	92	92	HIDABE95
55	671993	NAD(H)-specific isocitrate dehydrogenase gamma-subunit precursor [Homo sapiens] >gnl PID e219959 NAD (H)-specific isocitrate dehydrogenase gamma subunit precursor [Homo sapiens] >gij 302655 NAD+-isocitrate dehydrogenase gamma subunit [Homo sapiens] >gij 40	gnl PID e211919	1	993	91	91	HSJCA89
56	674618			223	312			HOVBX22
57	675027			789	1160			HSDII69
58	677202	vimentin [Homo sapiens] >sp Q15867 Q15867 VIMENTIN (FRAGMENT). Length = 354	gij 340232	705	896	100	100	HWACG51

59	678504	ORF YGR031w [Saccharomyces cerevisiae] >pir S64322 S64322 probable membrane protein YGR031w - yeast (Saccharomyces cerevisiae) Length = 342	gnl PID e2432 77	320	640	38	63	HCHAG27
60	678985	54 kDa protein [Homo sapiens] >gnl PID e1245514 p54nrb [Homo sapiens] >pir G01211 G01211 54 kDa protein - human >sp Q12786 Q12786 54 KDA PROTEIN. Length = 471 (AF036241) Na+/H+ exchange regulatory co-factor [Homo sapiens] >gi 3220019 (AF015926) ezrin-radixin-moesin binding phosphoprotein-50 [Homo sapiens] >sp O14745 O14745 EZRIN-RADIXIN-MOESIN BINDING PHOSPHOPROTEIN-50. Length = 358	gi 407308	358	1203	100	100	HCHOL54
61	682161	(AF036241) Na+/H+ exchange regulatory co-factor [Homo sapiens] >gi 3220019 (AF015926) ezrin-radixin-moesin binding phosphoprotein-50 [Homo sapiens] >sp O14745 O14745 EZRIN-RADIXIN-MOESIN BINDING PHOSPHOPROTEIN-50. Length = 358	gi 2920585	3	869	89	89	HCHAG19
62	683476	KDEL receptor [Homo sapiens] >pir S13293 S13293 KDEL receptor - human >sp P24390 P24390 HUMAN ER LUMEN PROTEIN RETAINING RECEPTOR 1 (KDEL RECEPTOR 1). Length = 212	gi 34031	1	132	100	100	HOFMM27
63	691146	KDEL receptor [Homo sapiens] >pir S13293 S13293 KDEL receptor - human >sp P24390 P24390 HUMAN ER LUMEN PROTEIN RETAINING RECEPTOR 1 (KDEL RECEPTOR 1). Length = 212	gi 34031	1	372	100	100	IIDAB02
64	693589	KDEL receptor [Homo sapiens] >pir S13293 S13293 KDEL receptor - human >sp P24390 P24390 HUMAN ER LUMEN PROTEIN RETAINING RECEPTOR 1 (KDEL RECEPTOR 1). Length = 212	gi 34031	1	393	100	100	HCHAS12

65	694991	B4B gene product [Homo sapiens] >gnl PID e265628 progression associated protein [Homo sapiens] >gij 1932786 epithelial membrane protein [Homo sapiens] >gij2506160 TMP [Homo sapiens] >sp P54849 EMPI_HUMAN EPITHELIAL MEMBRANE PROTEIN-1 (EMP-1) (TUMOR-ASSOCIA	gnl PID e1949 46	1	663	98	98	HRAAY77
66	698303	heat shock factor 1 [Homo sapiens] >pir A41137 A41137 heat shock transcription factor 1 - human >sp Q00613 HSF1_HUMAN HEAT SHOCK FACTOR PROTEIN 1 (HSF 1) (HEAT SHOCK TRANSCRIPTION FACTOR 1) (HSTF 1). Length = 529 filamin [Homo sapiens] Length = 2647	gij 184403	23	1168	85	85	HSHCASS
67	698669		gij 1203969	27	1274	98	98	HEGAR20
68	705696			321	458			HOFMP28
69	706393	vacuolar H+ ATPase proton channel subunit [Homo sapiens] >pir A39367 A39367 H+- transporting ATPase (EC 3.6.1.35) chain PKD1 - human Length = 155	gij 189676	119	604	84	85	HSKHIP64
70	707357			3	344			HOFMM35

71	707360	leucine aminopeptidase, LAP [cattle, kidney, Peptide, 513 aa] [Bos taurus] >pir A54338 APBOL leucyl aminopeptidase (EC 3.4.11.1), renal - bovine >sp P00727 AMPL_BOVIN CYTOSOL AMINOPEPTIDASE (EC 3.4.11.1) (LEUCINE AMINOPEPTIDASE) (LAP) (LEUCYL AMINOPEPTIDASE)	bbs I37417	1	447	81	89	HOFOF35
72	707375	serine/threonine protein kinase [Homo sapiens] >pir S23385 S23385 protein kinase (EC 2.7.1.37) cdc2-related PCTAIRE-1 - human >sp Q00536 KPT1_HUMAN SERINE/THREONINE-PROTEIN KINASE PCTAIRE-1 (EC 2.7.1.-). >sp G252370 G252370 CDC2-RELATED PROTEIN KINASE {CL	gi 36619	2	1582	92	92	HTOJQ73
73	707754			2	376			HLDBT45
74	711172			237	395			HOVCI40
75	712248	transcription factor AP-2 beta [Homo sapiens] >sp E286536 E286536 TRANSCRIPTION FACTOR AP-2 BETA. Length = 367	gn PID e286536	99	344	100	100	HKGCW94
76	715445	DNA-PK [Homo sapiens] >pir G02083 G02083 DNA-PK - human (fragment) >sp Q13337 Q13337 DNA-PK (FRAGMENT). Length = 930	gi 1017757	119	988	99	99	HLTDJ07
77	716362			221	688			HIBGBC77

78	716835	(AF036241) Na+/H+ exchange regulatory co-factor [Homo sapiens] >gi 3220019 (AF015926) ezrin-radixin-moesin binding phosphoprotein-50 [Homo sapiens] >sp O14745 O14745 EZRIN-RADIXIN-MOESIN BINDING PHOSPHOPROTEIN-50. Length = 358	gi 2920585	3	755	79	79	HCHAI81
79	716947	SRp55-2 [Homo sapiens] Length = 135	gi 1049084	2	145	100	100	HADDY71
80	717685	alpha-mannosidase [Homo sapiens] Length = 987	gi 1419374	2	1120	99	99	HIDPUOIS
81	719755			89	802			HCGAC54
82	720389	inducible membrane protein [Homo sapiens] >gi 806806 cell surface glycoprotein [Homo sapiens] >gi 1832296 metastasis suppressor [Homo sapiens] >pir 138942 A46493 metastasis suppressor KAI1 - human >sp P27701 CD82_HUMAN CD82 ANTIGEN (INDUCIBLE MEMBRANE PRO	gi 35833	1	594	65	67	HUVCR41
83	720903	cDNA isolated for this protein using a monoclonal antibody directed against the p27k prosomal protein [Homo sapiens] Length = 266	gnl P1D e103161	108	614	93	95	HFVIH35

84	721348	G6PD (AA 1-515) [Homo sapiens] >sp P11413 G6PD_HUMAN GLUCOSE-6-PHOSPHATE 1-DEHYDROGENASE (EC 1.1.1.49) (G6PD). {SUB 2-515} >gi 439445 glucose-6-phosphate dehydrogenase [Didelphis virginiana] {SUB 258-288} >sp O46666 O46666 GLUCOSE-6-PHOSPHATE DEHYDROGENAS	gi 31543	545	2065	93	93	HSHBL14
85	721562	pescadillo [Homo sapiens] >sp O00541 O00541 PESCADILLO. Length = 588	gi 2194203	32	811	99	99	HCFCK84
86	722775			409	1680			HCHAD52
87	724463			126	335			HOFMP50
88	727501	SWI/SNF complex 170 KDa subunit [Homo sapiens] >sp Q92923 Q92923 SWI/SNF COMPLEX 170 KDA SUBUNIT. Length = 1213	gi 1549241	1	1302	97	97	HL YBV46
89	728418	GTP binding protein [Mus musculus] >pir A39611 A39611 probable GTP-binding protein - mouse >sp P23249 MV10_MOUSE PROTEIN MOV-10. >gi 433685 gb 110 /Mov 10 locus gene product [Mus musculus] {SUB 1-45} Length = 1004	gi 53169	3	911	93	96	HSSEP09
90	728920	adipophilin [Homo sapiens] >sp Q99541 Q99541 ADIPOPHILIN (FRAGMENT). Length = 437	gnl PID e292752	2	751	89	89	HILDRQ71
91	732958			3	296			HPTYA52

92	733134	NF45 protein [Homo sapiens] >pir A54857 A54857 transcription factor NF-AT 45K chain - human >sp Q12905 Q12905 NF45 PROTEIN. Length = 406	gi 532313	84	1259	100	100	HHBHP80
93	734099			150	365			HBGDI44
94	734599			163	705			H6EED05
95	736019	ribosomal protein L11 [Homo sapiens] >gi 57678 ribosomal protein L11 [Rattus rattus] >pir S17351 RSRT11 ribosomal protein L11 precursor - rat >sp G3115334 G3115334 RIBOSOMAL PROTEIN L11. >sp D1026769 D1026769 RIBOSOMAL PROTEIN L11 (FRAGMENT). {SUB 17-52}	gi 3115334	3	608	100	100	HSEBB02
96	738268			45	233			HE2OC41
97	738911	(AF069291) hT41 [Homo sapiens] >sp G3687829 G3687829 HT41. Length = 505	gi 3687829	3	656	40	62	HCHCI12
98	739226			3	125			HADFY59
99	739527			3	752			HACCL62
100	740710	acyl-CoA synthetase-like protein [Homo sapiens] Length = 670	gn P1D1e3212 96	8	307	96	100	HPMFQ72

101	742980	serine-threonine specific protein phosphatase [Homo sapiens] >sp E1334695 E1334695 SERINE- THREONINE SPECIFIC PROTEIN PHOSPHATASE (EC 3.1.3.16). Length = 317	gnl PID e1334 695	3	182	81	86	HSKCE51
102	744331	ZINC FINGER PROTEIN {N- TERMINAL}. Length = 77	sp G632682 G 632682	432	791	62	80	HCHAH75
103	744751	collagen alpha 3(VI) chain precursor - human Length = 2970	pir S13679 C GHU3A	902	1189	100	100	HUJFFV63
104	745750			349	714			HCEHX66
105	746285			2016	2297			HNTNQ78
106	746416	(AB013357) 49 kDa zinc finger protein [Mus musculus] Length = 460	gnl PID d103 8083	113	391	97	97	HOFMO90
107	747851	(AF035387) C7-1 protein [Rattus norvegicus] >sp O54715 O54715 C7-1 PROTEIN. Length = 463	gi 2655418	3	974	78	80	HSSJG21
108	750632			252	449			HOGBF68
109	751315			423	608			HLTGN10
110	754009			408	773			HE8PN81
111	754634			525	1070			HUSGH70
112	756637	(AF044127) peroxisomal short-chain alcohol dehydrogenase [Homo sapiens] >sp G4105190 G4105190 PEROXISOMAL SHORT-CHAIN ALCOHOL DEHYDROGENASE. Length = 260	gi 4105190	38	586	89	91	HMWY27

113	756833		1	387			HCEDP17	
114	756878		127	399			IIBDE92	
115	757332	cytokeratin 8 [Homo sapiens] >gi 553163 keratin 8 [Homo sapiens] {SUB 1-231} Length = 482	35	235	96	100	HOFMI52	
116	760835	Pectinase gene transcriptional regulator. [Escherichia coli] >gnl PID d1015936 Pectinase gene transcriptional regulator. [Escherichia coli] >gi 1787806 (AE000250) putative transcriptional regulator L YSR- type [Escherichia coli] >pir A64907 A64907 hypoethi	3	434	100	100	HE9BW44	
117	761760	F45G2.10 [Caenorhabditis elegans] >sp O62252 O62252 F45G2.10 PROTEIN. Length = 160	3	527	61	81	HMWIF41	29
118	762520	B-myb protein (AA 1-700) [Homo sapiens] >pir S0199 S0199 transforming protein B-myb - human >sp P10244 MYBB_HUMAN MYB- RELATED PROTEIN B (B-MYB). Length = 700	77	520	100	100	HBJJIB76	
119	764461		2	211			HOFMH95	
120	764517	phosphomevalonate kinase [Homo sapiens] >sp Q15126 PMKA_HUMAN PHOSPHOMEVALONATE KINASE (EC 2.7.4.2) (PMKASE). {SUB 2-192} >gi 3445542 (AF026069) phosphomevalonate kinase [Homo sapiens] {SUB 33-192} Length = 192	260	877	100	100	HCGAA73	

121	765132	clk1; putative [Homo sapiens] >pir S53641 S53641 protein kinase clk1 (EC 2.7.1.-) - human >sp P49759 CLK1_HUMAN PROTEIN KINASE CLK1 (EC 2.7.1.-) (CLK). Length = 484	g 632964	1202	2251	99	99	HE9QA05
122	765667	(AF043250) mitochondrial outer membrane protein [Homo sapiens] >g 3941347 (AF043253) mitochondrial outer membrane protein [Homo sapiens] >g 4105703 (AF050154) D19S1177E [Homo sapiens] >sp G3941342 G3941342 MITOCHONDRIAL OUTER MEMBRANE PROTEIN. >sp G3941	g 3941342	144	1115	91	91	HCHOB54
123	767113	putative progesterone binding protein [Homo sapiens] >sp O00264 O00264 PUTATIVE PROGESTERONE BINDING PROTEIN. Length = 195	gn PID e3141 74	66	677	93	93	HNTMW26
124	767204	cytochrome P45011C4 [Oryctolagus cuniculus] >pir S20227 S20227 cytochrome P450 2C4 - rabbit (fragment) >sp Q29507 Q29507 CYTOCHROME P450 (EC 1.14.14.1) (FRAGMENT). Length = 145	g 164933	3	581	43	61	HCHIAN75
125	767400			2	1057			HSYBI74

126	767962	proteasome subunit C3 [Homo sapiens] >pir S15970 SNHUC3 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C3 - human >sp P25787 PRC3_HUMAN PROTEASOME COMPONENT C3 (EC 3.4.99.46) (MACROPAIN SUBUNIT C3) (MULTICATALYTIC ENDOPEPTIDASE COMPLEX SUBUNIT (AB002086) p47 [Rattus norvegicus] >gn PID e294068 XY40 protein [Rattus norvegicus] >sp Q35987 Q35987 P47, COMPLETE CDS. Length = 370 adenine phosphoribosyltransferase [Homo sapiens] >gi 28819 adenine phosphoribosyltransferase (aprt) [Homo sapiens] >pir S06232 RTHUA adenine phosphoribosyltransferase (EC 2.4.2.7) - human >sp P07741 APT_HUMAN ADENINE PHOSPHORIBOSYLTRANSFERASE (EC 2.4.2.7)	gn PID d100 1115	3	722	100	100	HABAF63
127	768040		gn PID d102 2509	119	661	84	89	HSRDI53
128	769956		gi 178867	2	592	100	100	HIUFFC71
129	770133			958	1236			HUSAX93
130	770289	ALDH7 [Homo sapiens] >pir I38669 I38669 ALDH7 - human >sp P43353 DHA7_HUMAN ALDEHYDE DEHYDROGENASE 7 (EC 1.2.1.5). >sp G601780 G601780 ALDH7. Length = 468	gi 601780	194	340	65	69	HCHAO38

131	771964	(AD000092) human RAD23A homolog [Homo sapiens] >gnl PID d1005299 HHR23A protein [Homo sapiens] >pir S44443 S44443 RAD23 protein homolog2 - human Length = 363 B-myb protein (AA 1-700) [Homo sapiens] >pir S01991 S01991 transforming protein B-myb - human >sp P10244 MYBB_HUMAN MYB- RELATED PROTEIN B (B-MYB). Length = 700	gnl 1905912	29	1165	76	76	HAMGD77
132	772582	zinc finger protein [Homo sapiens] >pir I38620 I38620 zinc finger protein ZNF155 - human (fragment) Length = 139	gnl 29472	150	974	99	99	HYAAO51
133	773387	novel serine protease, PRSS11 [Homo sapiens] >gnl PID d1014012 serin protease with IGF-binding motif [Homo sapiens] >sp Q92743 Q92743 NOVEL SERINE PROTEASE, Length = 480 protein of unknown function [Homo sapiens] >pir C35826 C35826 hypothetical protein A, 13K - human >sp Q00994 HG74_HUMAN OVARIAN GRANULOSA CELL 13.0 KD PROTEIN HGR74. Length = 111	gnl PID e2751 86	3	1217	100	100	HKAD115
134	773827		gnl 189379	303	623	75	75	HEGAC01

136	774636	glutathione transferase [Homo sapiens] >pir A39375 A39375 glutathione transferase (EC 2.5.1.18) class mu, GSTM2 - human >sp P28161 GTM2_HUMAN GLUTATHIONE S-TRANSFERASE MU 2 (EC 2.5.1.18) (GSTM2-2) (CLASS-MU). {SUB 2-218} >gnl PID e33921 glutathione transf	gi 183301	61	747	98	98	HISDV78
137	775339	SWI/SNF complex 60 KDa subunit [Homo sapiens] >sp Q92924 Q92924 SWI/SNF COMPLEX 60 KDA SUBUNIT. Length = 435	gi 1549243	3	320	98	100	HSIGB35
138	775582			448	705			HEPNB30
139	775779	(AJ000332) Glucosidase II [Homo sapiens] >sp Q14697 Q14697 GLUCOSIDASE II PRECURSOR (K1AA0088). >gnl PID d1008224 The ha1225 gene product is related to human alpha- glucosidase. [Homo sapiens] {SUB 2-944} Length = 944	gnl PID e3281 43	1	1695	98	98	HLWAS86
140	777809	cysteine-rich protein 2 [Homo sapiens] >gnl PID d1008288 ESP1/CRP2 [Homo sapiens] >pir G02090 G02090 cysteine-rich protein 2 - human >sp P52943 CRP2_HUMAN CYSTEINE- RICH PROTEIN 2 (CRP2) (ESP1 PROTEIN). Length = 208	gi 1399028	202	681	99	100	HSPMB57
141	778927	valyl-tRNA synthetase [Homo sapiens] >pir S17675 S17675 valine--tRNA ligase (EC 6.1.1.9) - human Length = 1265	gi 31545	1843	3282	88	88	HMVBW39

142	779262		1	288			HTENK29
143	779392		2	181			HE2FO87
144	780149	proteasome activator hPA28 suunit beta [Homo sapiens] >pir 53518 53518 proteasome activator hPA28 suunit beta - human >sp Q15129 Q15129 PROTEASOME ACTIVATOR HPA28 SUUNIT BETA. >sp G693763 G693763 PA28=REGULATORS OF THE 20 S PROTEASOME {PEPTIDE 15}. {SUB	233	955	93	93	HSPMF83
145	780583		8	607			HHIEW04
146	780960		232	576			HOEBN65
147	781469	radixin [Homo sapiens] >pir A46127 A46127 radixin - human Length = 583	1	303	100	100	HNTRA25
148	781556		116	190			HOSAW82
149	781771		1	822			HE6EO05
150	782033	histone H2A [Gallus gallus] Length = 129	146	544	98	100	HULCC66
151	782105		606	1064			HKAKV16

152	782122	high density lipoprotein binding protein [Homo sapiens] >pir A44125 A44125 high density lipoprotein-binding protein, 110K - human >sp Q00341 HBP_HUMAN HIGH DENSITY LIPOPROTEIN BINDING PROTEIN (HDL-BINDING PROTEIN). >sp G1478463 G1478463 VIGILIN=KH PROTEIN	gj 183892	3	983	95	95	HSRAB32
153	783135	zinc finger protein [Homo sapiens] >sp O00488 O00488 ZINC FINGER PROTEIN. Length = 116	gn P1D1d102 1201	3	500	97	99	HCHCB61
154	783245			3	341			HTSFV77
155	783247			95	391			HBMGMD18
156	783413	D9 splice variant 3 [Mus musculus] >sp O08695 O08695 D9 SPLICE VARIANT 3. Length = 169	gj 2071991	1	591	80	88	HEBFR23
157	784407			45	185			HFKAA09
158	784548	nuclear RNA helicase (DEAD family) [Homo sapiens] >pir I37201 I37201 nuclear RNA helicase (DEAD family) BAT1 - human >sp Q13838 HE47_HUMAN PROBABLE ATP-DEPENDENT RNA HELICASE P47. >gj 2739119 (AF029061) BAT1 [Homo sapiens] {SUB 145-428} >gj 971677 express	gj 587146	676	1020	90	92	HSRFZ85

159	785075	KIAA0100 is a human counterpart of mouse e1 gene. [Homo sapiens] >sp Q14667 Q14667 KIAA0100 (HUMAN COUNTERPART OF MOUSE E1 GENE). Length = 2092	gnl PID d100 8477	72	1109	93	93	HDPFX40
160	785677	(AC004084) similar to DNA-DIRECTED RNA POLYMERASE II 13.3 KD POLYPEPTIDE; 98% similar to P5243 (PID:g I710661) [Homo sapiens] >sp O43375 O43375 SIMILAR TO DNA-DIRECTED RNA POLYMERASE II 13.3 KD POLYPEPTIDE (FRAGMENT). Length = 105	gi 2822158	1	273	95	100	HBSAJ50
161	786238			2	994			HOVCA75
162	786389			3	1124			ILLJDU61
163	786929	(AJ224442) methyltransferase [Homo sapiens] >sp O43709 O43709 METHYLTRANSFERASE. Length = 220 PIPPin protein [Rattus norvegicus] >pir JC4588 JC4588 RNA-binding protein PIPPin - rat >sp Q63430 Q63430 PIPPIN PROTEIN. Length = 154	gnl PID e1253 426	123	404	86	95	IIOFNV27
164	786932		gi 1050754	2	490	76	87	HUSYH27
165	787078	HER2 receptor [Homo sapiens] >gi 553282 c-erb-2 protein [Homo sapiens] {SUB 737-1031} >gi 553332 HER-2/neu [Homo sapiens] {SUB 1-191} >gi 183989 HER2 receptor (AA at 3) [Homo sapiens] {SUB 740-910} >gi 182169 c-erb B2/neu protein [Homo sapiens] {SUB 1081-	gi 306840	236	1114	79	79	HCHND12

166	787139			230	625		HBCBA06
167	787283			3	656		HFOYO96
168	788761	MAL3P6.24 [Plasmodium falciparum] >sp O77371 O77371 MAL3P6.24 PROTEIN. Length = 1017	gnl P D e 331 909	2	700	36	HTXFK57
169	788988	(AF023611) Dim1p homolog [Homo sapiens] >sp O14834 O14834 DIM1P HOMOLOG. Length = 142	gi 2565275	70	417	98	HUSGH90
170	789092			2	400		H6EBE80
171	789298	(AF044311) gamma-synuclein [Homo sapiens] >gi 3642775 (AF017256) persyn [Homo sapiens] >gi 3642903 (AF037207) persyn [Homo sapiens] >sp O76070 O76070 PERSYN. Length = 127	gi 3347842	1	489	82	HTSFM20
172	789299			205	381		HBGDD91
173	789718			233	580		IIBGBT30
174	789957	beta-hexosaminidase alpha chain [Homo sapiens] >pir A23561 AOHUBA beta-N- acetylhexosaminidase (EC 3.2.1.52) alpha chain precursor - human >sp P06865 HEXA_HUMAN BETA- HEXOSAMINIDASE ALPHA CHAIN PRECURSOR (EC 3.2.1.52) (N-ACETYL- BETA-GLUCOSAMINIDASE) (BETA-	gi 179458	750	1619	99	HISEM44

175	789977	arginyl-tRNA synthetase, ArgRS [human, ataxia-telangiectasia patients, EBV-lymphoblastoid cells, Peptide, 659 aa] [Homo sapiens] >pir JC4365 JC4365 arginine--tRNA ligase (EC 6.1.1.19) - human Length = 659	bbs 173838	25	2019	94	95	HIMEIU30
176	790285	HCG V [Homo sapiens] >sp O60927 O60927 HCG V. Length = 126	gij 3176438	44	391	85	85	HDPC88
177	790509	human elongation factor-1-delta [Homo sapiens] >pir S34626 S34626 translation elongation factor eEF-1 delta chain - human >sp P29692 EF1D_HUMAN ELONGATION FACTOR 1-DELTA (EF-1-DELTA). Length = 281	gij 38522	227	1108	63	64	HPMGB64
178	790775			950	1351			HJAAO21
179	790888	(AF036956) neuroblastoma apoptosis-related RNA binding protein [Homo sapiens] >sp G4104559 G4104559 NEUROBLASTOMA APOPTOSIS-RELATED RNA BINDING PROTEIN. Length = 490	gij 4104559	2	274	100	100	HE8QE19
180	791506			2	205			HOFMB93
181	791649			3	359			HGBBH10
182	791802			165	695			HWLRH03

183	792002	ADP-ribosylation factor [Homo sapiens] >gi 2088529 ADP-ribosylation factor 5 [Homo sapiens] >gi 438870 ADP- ribosylation factor 5 [Rattus norvegicus] >gnl PID d1014187 ARF5 [Mus musculus] >pir A23741 A23741 ADP-ribosylation factor 5 - human >pir JC4949 JC4	gi 178987	2	635	100	100	HHENT53
184	792291	see GenBank Accession Number U01184 for cDNA; similar to Drosophila melanogaster fil in GenBank Accession Number U01182 and Caenorhabditis elegans fil homolog in GenBank Accession Number U01183 [Homo sapiens] >sp Q13045 Q13045 FLIGHTLESS-1 PROTEIN HOMOL	gi 2138290	843	3329	96	96	HDPIT69
185	792371			3	665			HUSJW77
186	792660	(AF044773) breakpoint cluster region protein 1 [Homo sapiens] >sp O60558 O60558 BREAKPOINT CLUSTER REGION PROTEIN 1. Length = 138	gi 3002951	116	406	100	100	HCHMC26
187	792782			41	838			HTXJB38
188	792890	(AF001846) lymphoid phosphatase LyP1 [Homo sapiens] >sp G4100632 G4100632 LYMPHOID PHOSPHATASE LYPI. Length = 808	gi 4100632	2	994	90	90	HHESJ29
189	792931			1	576			HEGAW71

190	792943	myosin heavy chain kinase B [Dictyostelium discoideum] >sp P90648 KMHIB_DICDI_MYOSIN HEAVY CHAIN KINASE B (EC 2.7.1.129) (MHCK B). Length = 732	gi 1903458	3	1247	43	68	IIDPRZ79
191	793104			107	250			HKGAJ80
192	793445	desmoyokin - human (fragments) >sp Q09666 AHNK_HUMAN NEUROBLAST DIFFERENTIATION ASSOCIATED PROTEIN AHNAK (DESMOYOKIN) (FRAGMENTS). >gi 178281 AHNAK_nucleoprotein [Homo sapiens] {SUB 1-1683} >gi 897824 AHNAK gene product [Homo sapiens] {SUB 1684-2960} Leng	pir A45259 A 45259	1	723	92	92	HDTEJ86
193	793446			25	255			HIIBGY94
194	793639	(AF044959) NADH:ubiquinone oxidoreductase NDUFS6 subunit [Homo sapiens] >sp O75380 NUMM_HUMAN NADH-UBIQUINONE OXIDOREDUCTASE 13 KD-A SUBUNIT PRECURSOR (EC 1.6.5.3) (EC 1.6.99.3) (COMPLEX I-13KD-A) (CI-13KD-A). Length = 124 100 kDa protein [Rattus norvegicus] >pir S22659 S22659_hypothetical protein, 100K - rat >sp Q62671 100K_RAT 100 KD PROTEIN (EC 6.3.2.-). Length = 889	gi 3348137	1	411	100	100	HLJB172
195	794213		gi 55535	326	691	93	95	HLWCN67
196	795858			1020	1205			HLVDY53

197	795955	c-myc binding protein [Homo sapiens] >sp Q99471 MM1_HUMAN C-MYC BINDING PROTEIN MM-1. >sp D1014706 D1014706 C-MYC BINDING PROTEIN. Length = 167	gn P D d I01 4706	31	507	100	100	HUSXX36
198	796359	ribosomal protein L7a large subunit [Homo sapiens] >gi 34203 L7a protein [Homo sapiens] >gi 35512 PLA-X polypeptide [Homo sapiens] >gi 36647 ribosomal protein L7a [Homo sapiens] >gi 56956 ribosomal protein L7a (AA 1-266) [Rattus rattus] >pir S19717 R5HU7A	gi 337495	19	297	100	100	HOFNW79
199	796555	DJ366N23.3 (KIAA0173 AND TUBULIN- TYROSINE LIGASE LIKE) (FRAGMENT). Length = 278	sp O75653 O7 5653	1	1086	44	62	HLWEW04
200	796675	PEG1/MEST [Homo sapiens] >sp O15007 O15007 PEG1/MEST GENE MRNA. Length = 335	gn P D e 3070 37	44	1027	100	100	HSICR25
201	796743	(AF022229) translation initiation factor 6 [Homo sapiens] >gn P D e 304603 b4 integrin interactor [Homo sapiens] >gi 3335506 (AF047433) b(2)gcn homolog [Homo sapiens] >sp P56537 IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT	gi 2809383	30	842	100	100	H6EDU12
202	796792			198	461			HDTII72
203	799668			166	303			HODBC01
204	799669			2	310			HOGAV29

205	799673		2	310		HOFMNS3
206	799674		130	1044		HCHMI60
207	799678	ribosomal protein L18a [Homo sapiens] >gi 3702270 (AC005796) ribosomal protein L18a [Homo sapiens] >gnl PI D1029536 (AB007175) ribosomal protein L18a [Homo sapiens] {SUB 111-176} Length = 176	40	345	98	HOFNL25
208	799728		3	179		HBGBG75
209	799748		1	660		IIC11MQ24
210	799760	o361 [Escherichia coli] >gi 1790125 (AE000446) orf, hypothetical protein [Escherichia coli] >pir C65171 C65171 hypothetical 41.0 kD protein in ibpA-gyrB intergenic region - Escherichia coli (strain K-12) Length = 361	1	357	99	11BGBF66
211	799805		2	118		HBGDA22
212	800296	CDC37 homolog [Homo sapiens] >gi 375485 CDC37 homolog [Homo sapiens] >pir G02313 G02313 CDC37 homolog - human >sp Q16543 Q16543 CDC37 HOMOLOG. Length = 378	2	802	89	HDABE68

213	800327	ADP-ribosylation factor-like protein 2 [Homo sapiens] >pir A48259 A48259 ADP- ribosylation factor-like 2 - human >sp P36404 ARL2_HUMAN ADP- RIBOSYLATION FACTOR-LIKE PROTEIN 2. >sp G425655 G425655 ARL2=ADP-RIBOSYLATION FACTOR HOMOLOG. Length = 184	gj 3009501	25	645	99	99	HCHPG41
214	800816			115	351			HODCV09
215	800835	(AF071538) Ets transcription factor PDEF [Homo sapiens] >sp G4007418 G4007418 ETS TRANSCRIPTION FACTOR PDEF. Length = 335	gj 4007418	3	881	96	96	HETJP29
216	805429	RanGAP1 [Homo sapiens] >pir JC5300 JC5300 Ran GTPase activator 1 - human Length = 587	gj 575268	3	683	90	90	HKABS06
217	805458	(AF044221) HCG-1 protein [Homo sapiens] >sp G4105252 G4105252 HCG-1 PROTEIN. Length = 117	gj 4105252	745	1122	100	100	HDQEV55
218	805478			60	644			HDQGR35
219	805805	19 kDa subunit of NADH:ubiquinone oxidoreductase complex (complex I) [Bos taurus] >pir S16208 S16208 NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) 19K chain - bovine >sp P42029 NUPM_BOVIN NADH- UBIQUINONE OXIDOREDUCTASE 19 KD SUBUNIT (EC 1.6.5.3) (EC 1.6.99	gj 599681	2	478	87	90	HOFMH12
220	806486			3	62			HFXJC33

221	806498		518	1741		HIBCA25		
222	806819	acidic ribosomal phosphoprotein (P0) [Homo sapiens] >gi 2935618 (AC004263) 60S ACIDIC RIBOSOMAL PROTEIN; match to P05388 (PID:gi 33041) [Homo sapiens] >pir A27125 R5HUP0 acidic ribosomal protein P0 - human >sp D1026785 D1026785 RIBOSOMAL PROTEIN P0 (FRAGME	gi 190232	3	866	81	84	HOFAC09
223	810870	thrombospondin-4 [Homo sapiens] >pir A55710 TSHUP4 thrombospondin 4 precursor - human Length = 961	gi 311626	2	1333	99	99	HBOEB83
224	811730			2	979			HCHPJ26
225	813025	heat shock protein 86 [Homo sapiens] >sp Q14568 Q14568 HEAT SHOCK PROTEIN 86 (FRAGMENT). Length = 312	gi 292162	106	492	88	89	IIOFMD78
226	813233	co-beta glucosidase precursor [Homo sapiens] >gi 337762 prosaposin [Homo sapiens] >gi 337756 sphingolipid activator precursor [Homo sapiens] Length = 524	gi 183231	1	468	81	90	IIOFMF17
227	813262			1	345			HFKCA89
228	815637	(AC004003) serine/threonine kinase RICK; match to protein AF027706 (PID:gi 3123887) and mRNA AF027706 (NID:gi 3123886) [Homo sapiens] >gi 3290172 (AF064824) CARD-containing ICE associated kinase [Homo sapiens] >gi 3342910 (AF078530) receptor	gi 3264574	3	461	92	92	HNHDS66

interacting prote

229	815853	calcyphosine [Homo sapiens] >gi 3075376 (AC004602) CAYP_HUMAN; RD25 [Homo sapiens] >sp Q13938 CAYP_HUMAN CALCYPHOSINE. Length = 189	gnl PID e2458 72	8	667	100	100	HLHAY85
230	815999	S100 calcium-binding protein A13 (S100A13) [Homo sapiens] >pir JC5064 JC5064 S-100 calcium-binding protein A13 - human Length = 98	gnl PID e2682 53	68	421	42	70	HKABX07
231	823427			1	927			HTLGL50
232	823704	(AC004770) BC269730_2 [Homo sapiens] >sp O60427 O60427 BC269730_2. Length = 444	gi 3169158	3	860	67	80	HDABC49
233	824798			307	858			HDQ GK75
234	825018			2	1924			HETIS29
235	825076	Whole ORF continues from bp19 (right after 'tag') to bp1596 ('tag'); similar to chinese hamster phosphatidylserine synthase. [Homo sapiens] Length = 473	gnl PID d100 4031	2	1549	92	92	HE9PJ48

236	825787	EXT2 [Homo sapiens] >gi 1621113 hereditary multiple exostoses gene 2 protein [Homo sapiens] >gi 1519605 multiple exostosis 2 [Homo sapiens] >sp Q93063 EXT2_HUMAN EXOSTOSIN-2 (PUTATIVE TUMOUR SUPPRESSOR PROTEIN EXT2) (MULTIPLE EXOSTOSES PROTEIN 2). Length	gi 1518042	305	2293	100	100	HIFONV84
237	826116	BETA CRYSTALLIN S (GAMMA CRYSTALLIN S). >gi 557548 crystallin [Homo sapiens] {SUB 19-106} Length = 177	sp P22914 CR BS_HUMAN	392	682	86	87	HAIJAE27
238	826147	neural specific protein CRMP-2 [Bos taurus] >sp O02675 DPY2_BOVIN DIHYDROPYRIMIDINASE RELATED PROTEIN-2 (DRP-2) (NEURAL SPECIFIC PROTEIN NSP60). Length = 572	gi 1916227	3	503	98	98	HICEPT06
239	827020	(AF027954) Bcl-2-related ovarian killer protein [Rattus norvegicus] >gi 2689660 (AF027707) apoptosis activator Mtd [Mus musculus] >sp Q35425 O35425 BCL-2- RELATED OVARIAN KILLER PROTEIN. Length = 213	gi 2645560	12	539	95	97	HHFHE17
240	827586	calmodulin [Plasmodium falciparum] >gi 160128 calmodulin [Plasmodium falciparum] >pir B45594 MCZQF calmodulin - Plasmodium falciparum >sp P24044 CALM_PLAFA CALMODULIN. Length = 149	gi 385234	85	495	49	76	HCHMW40

241	827732	alternate name ygiG; ORF_f123 [Escherichia coli] >gij1789438 (AE000387) putative kinase [Escherichia coli] >pir H65093 H65093 ygiG protein - Escherichia coli (strain K-12) >sp P31055 FOLB_ECOLI PROBABLE DIHYDRONEOPTERIN ALDOLASE (EC 4.1.2.25) (DHNA). {SUB	gij1882580	181	282	91	95	HBGDE81
242	827735			541	708			HHEDU22
243	827740			716	838			HBNAP17
244	827808			86	1657			HMELR44
245	828251	(AB016869) p70 ribosomal S6 kinase beta [Homo sapiens] >sp D1035383 D1035383 P70 RIBOSOMAL S6 KINASE BETA. Length = 495	gnl PID d103 5383	134	949	91	91	INGOL64
246	828357			1	768			HKIYP61
247	828449			1	723			HBXCZ22
248	828612	syntaxin 5 [Homo sapiens] >pir G01817 G01817 syntaxin 5 - human Length = 301	gij1886071	68	460	100	100	HNHMY58
249	828647	laminin beta 2 chain [Homo sapiens] >sp P55268 LMB2_HUMAN LAMININ BETA-2 CHAIN PRECURSOR (S- LAMININ). Length = 1798	gnl PID e2132 86	299	2254	85	85	HRABB47

250	828698	galactokinase [Homo sapiens] >gi 1929895 galactokinase [Homo sapiens] >sp P51570 GAL1_HUMAN GALACTOKINASE 1 (EC 2.7.1.6). >gi 3603423 (AF084935) galactokinase [Homo sapiens] {SUB 1-264} Length = 392	gi 1002507	3	1220	83	83	HKGAU37
251	828962	secretory protein [Homo sapiens] >gi 940946 intestinal trefoil factor [Homo sapiens] >pir A48284 A48284 intestinal trefoil factor 3 precursor - human >sp Q07654 ITF_HUMAN INTESTINAL TREFOIL FACTOR PRECURSOR (HPI.B). Length = 80	gi 402483	2	259	78	78	HCHMR52
252	828982	unnamed protein product [unidentified] >gi 189500 p62 [Homo sapiens] >pir A38219 A38219 GAP-associated tyrosine phosphoprotein p62 - human >sp Q07666 Q07666 GAP-ASSOCIATED TYROSINE PHOSPHOPROTEIN P62. >gnl PID e1259626 unnamed protein product [unidentifie	gnl PID e1259 622	1	1176	85	85	HE9PC52
253	829282			289	828			HCHOB95
254	829368			279	512			HWGAA79
255	829751			2	418			HCHMB33
256	829773	(AF109906) G9A [Mus musculus] >sp G3986768 G3986768 G9A. Length = 1000	gi 3986768	26	862	97	98	HMWBV67

257	829934	precursor polypeptide (AA -21 to 782) [Homo sapiens] >pir A35954 A35954 endoplasmin precursor - human >sp P14625 ENPL_HUMAN ENDOPLASMIN PRECURSOR (94 KD GLUCOSE-REGULATED PROTEIN) (GRP94) (GP96 HOMOLOG) (TUMOR REJECTION ANTIGEN 1). Length = 803 dynamitin [Homo sapiens] >sp Q13561 DYNC_HUMAN DYNACTIN, 50 KD ISOFORM (50 KD DYNEIN-ASSOCIATED POLYPEPTIDE) (DYNAMITIN). Length = 406	gi 37261	1142	2356	94	94	HFIIJ68
258	829942		gi 255188	15	1409	85	85	HUFBF69
259	829951			119	262			HIBGBA32
260	830173	death associated protein 5 [Homo sapiens] >sp O60877 O60877 DEATH ASSOCIATED PROTEIN 5. Length = 907	gi PID e1298 888	51	2870	90	90	HETIX39
261	830200			3	638			HIBGMF83
262	830365	mevalonate pyrophosphate decarboxylase [Homo sapiens] >sp P53602 ER19_HUMAN DIPHOSPHOMEVALONATE DECARBOXYLASE (EC 4.1.1.33) (MEVALONATE PYROPHOSPHATE DECARBOXYLASE). Length = 400	gi 235682	56	1291	95	95	HUSIG21
263	830456			215	397			HCFBN01

264	830549	guanine nucleotide-binding regulatory protein-beta-2 subunit [Homo sapiens] >gil339935 transducin beta-2 subunit [Homo sapiens] >gil3135310 (AF053356) GNB2 [Homo sapiens] >pir B26617 RGHUB2 GTP-binding regulatory protein beta-2 chain - human >sp P11016 GB	gil386751	1	729	100	100	100	1HDPM12
265	830602			24	461				HTLDJ82
266	830610	zyxin [Homo sapiens] >gnl PID e223417 zyxin [Homo sapiens] >pir G02845 G02845 zyxin - human Length = 572	gnl PID e2182 60	956	1855	94	94	94	1HDPRN35
267	830644	(AF104260) hiwi [Homo sapiens] >sp G4038413 G4038413 HIWI (FRAGMENT). Length = 523	gil4038413	2	391	99	99	99	HTTEU95
268	830707			3	623				HETCJ14
269	830709			2	304				HSSGN20
270	830733			540	725				HSNAD86
271	830768	carboxylesterase hCE-2 [Homo sapiens] >sp Q16859 Q16859 CARBOXYLESTERASE (EC 3.1.1.1) (AL1-ESTERASE) (B-ESTERASE) (MONOBUTYRASE) (COCAINE ESTERASE) (PROCAINE ESTERASE) (METHYLBUTYRASE). Length = 550	gil1407780	623	2269	99	99	99	1HDPMX44
272	830855			1	465				HJPC06

273	830949		2457	2903		HCE5J35
274	830965		139	792		HI01IC/A01
275	830973		354	557		HR0DL42
276	830979	THIOREDOXIN REDUCTASE 2. Length = 526	753	1454	81	HOGCC93
277	830989	La protein [Homo sapiens] >gi 36415 ribonucleoprotein SS-B/La (AA 1-408) [Homo sapiens] >pir A31888 A31888 ribonucleoprotein La - human >sp P05455 LA_HUMAN LUPUS LA PROTEIN (SJOGREN SYNDROME TYPE B ANTIGEN (SS-B)) (LA RIBONUCLEOPROTEIN) (LA AUTOANTIGEN).	3	1382	87	HDQFZ49
278	831134		2	241		HBXEB46
279	831200		3	773		HADXB20
280	831260		892	1095		HLWBR58
281	831531	transcription factor [Homo sapiens] >gi 37058 IIB protein [Homo sapiens] >pir S17654 TWHU2B transcription initiation factor IIB - human >bbs 112738 S300-II, TFIIIB=transcription factor [human, Peptide Partial, 311 aa] [Homo sapiens] {SUB 6-316} Length = 31	93	1172	95	HHPGX85
282	831665		2	1093		HSKDH81

283	831724			1	468				HFEBQ94
284	831884	(AF034800) liprin-alpha3 [Homo sapiens] >sp G3309535 G3309535 LIPRIN- ALPHA3 (FRAGMENT). Length = 443	gij 3309535	20	469	90			HDTGO74
285	831897	laminin B1 [Homo sapiens] >gij 186876 laminin B1 [Homo sapiens] >gij 186913 laminin B1 [Homo sapiens] >pir S13547 MMHUB1 laminin chain B1 precursor - human >sp P07942 LMB1_HUMAN LAMININ BETA-1 CHAIN PRECURSOR (LAMININ B1 CHAIN). Length = 1786	gij 186837	1	1581	92			HSKHIV84
286	831922			499	684				HDQIB68
287	831963			188	319				HDPCS84
288	832074	gluconate kinase [Escherichia coli] >gij 1790719 (AE000497) gluconate kinase, thermosensitive glucokinase [Escherichia coli] >pir S56494 S56494 gluconokinase (EC 2.7.1.12) gntV - Escherichia coli >sp P39208 GNTV_ECOLI THERMOSENSITIVE GLUCONOKINASE (EC 2.7.	gij 537110	1	579	42	58		HCRNT71
289	832266			71	433				HNGJU70
290	832309			1891	2226				HBJDT21
291	832342	fatty acid amide hydrolase [Homo sapiens] >sp O00519 O00519 FATTY ACID AMIDE HYDROLASE. Length = 579	gij 2149156	9	224	97	100		HBGDP82

292	832351	unknown product specific to adipose tissue [Homo sapiens] >sp Q15847 Q15847 HYPOTHETICAL 7.9 KD PROTEIN. Length = 76	gnl P1D1d100 8821	47	298	68	68	HFABE30
293	832352	unknown product specific to adipose tissue [Homo sapiens] >sp Q15847 Q15847 HYPOTHETICAL 7.9 KD PROTEIN. Length = 76	gnl P1D1d100 8821	89	277	92	94	HOEKX93
294	832434	Cks1 protein homologue [Homo sapiens] >pir A36670 A36670 protein kinase cdc2 complex subunit CKS1 - human >sp P33551 CKS1_HUMAN CYCLIN- DEPENDENT KINASES REGULATORY SUBUNIT 1 (CKS-1). Length = 79	gi 29977	78	335	100	100	HFNAB43
295	832490	growth arrest and DNA-damage-inducible protein [Homo sapiens] >gi 403128 [Human gadd45 gene, complete cds.], gene product [Homo sapiens] >pir A39617 A39617 DNA-damage-inducible protein gadd45 - human >sp P24522 GA45_HUMAN GROWTH ARREST AND DNA- DAMAGE-INDU	gi 182940	220	798	98	100	HKAKL21
296	832573			30	629			HCHOY13
297	832580	pS2 protein [Homo sapiens] >gi 35707 pS2 precursor [Homo sapiens] >gnl P1D1e223341 pS2 [Homo sapiens] >pir A26667 A26667 pS2 protein precursor - human >gi 182204 estrogen receptor [Homo sapiens] {SUB 2-84} Length = 84	gi 35718	45	362	100	100	H2LAR67

298	833394		274	588					HBGMC47
299	835355	(AF060567) sushi-repeat protein [Homo sapiens] >sp O60687 O60687 SUSHI-REPEAT PROTEIN. Length = 465	3	1295	99	100			HUSAU05
300	835497	(AJ006064) coronin-like protein [Rattus norvegicus] >sp O89046 O89046 CORONIN-LIKE PROTEIN. Length = 484	334	1584	96	99			HLDDS71
301	835728		2	871					HODAK21
302	835978		643	2019					ITLLEB03
303	836091	PDC-E2 precursor (AA -54 to 561) [Homo sapiens] >pir S01783 XXHIU dihydrolipoamide S-acetyltransferase (EC 2.3.1.12) precursor - human (fragment) >gi 345030 Human 70kd mitochondrial antigen of PBC [unidentified] {SUB 179-500} >sp G254062 G254062 PYRUVATE D	546	2114	99	99			I12CBW86
304	836274	Id4 [Homo sapiens] >gnl PID e266418 helix-loop-helix protein [Homo sapiens] >gnl PID e1359205 (AL022726) dJ625H18.1 (ID4 Helix-loop-helix DNA binding protein) [Homo sapiens] >gnl PID e266418 helix-loop-helix protein [Homo sapiens] >pir G01855 G01855 Id4 -	2	334	98	98			HCLBP52

305	836731	(AF075599) ubiquitin conjugating enzyme 12 [Homo sapiens] >gnl PID d1034111 (AB012191) Nedd8-conjugating enzyme hUbc12 [Homo sapiens] >sp O76069 O76069 UBIQUITIN- CONJUGATING ENZYME E2 (EC 6.3.2.19) (UBIQUITIN-PROTEIN LIGASE) (UBIQUITIN CARRIER PROTEIN). L prolyl 4-hydroxylase alpha (II) subunit [Homo sapiens] >sp O15460 O15460 PROLYL 4-HYDROXYLASE ALPHA (II) SUBUNIT (II). Length = 535	gnl 3309661	2	571	100	100	HFXAZ01
306	838014			3	1574	99	99	HTEHY24
307	838874		gi 2439985	271	546			HFPEZ63
308	839120	peptide transporter [Homo sapiens] >pir S13427 A41538 ATP-binding cassette transporter TAP1 - human >gi 34636 ABC- transporter [Homo sapiens] {SUB 61-808} >gi 930122 Y3 gene product [Homo sapiens] {SUB 183-612} Length = 808	gi 36061	100	2169	90	90	HINFY03
309	839611			548	793			HAMF154
310	840138	start position 1 [Homo sapiens] >sp E1335356 E1335356 ASMTL PROTEIN. >gnl PID e1335357 start position 2 [Homo sapiens] {SUB 59-629} Length = 629	gnl PID e1335 356	1	1800	92	93	HFIHW86

311	840616	Homology with Squid retinal-binding protein (PIR Acc. No. A53057) [Caenorhabditis elegans] >sp Q22467 Q22467.T13H5.2.PROTEIN. Length = 1254	gnl PID e1349 397	3	1607	73	86	HMSCY51
312	840780	unknown [Saccharomyces cerevisiae] >pir S58704 S58704.probable membrane protein YIL003w - yeast (Saccharomyces cerevisiae) >gil 558401.incomplete orf, len: 160, CAl: 0.09 similar to MRP_ECOLI P21590 39.9 KD PROTEIN [Saccharomyces cerevisiae] {SUB 1-158} >g	gil 763343	17	880	57	80	H6EDY61
313	840857	(AF071059) zinc finger RNA binding protein [Mus musculus] >sp O88532 O88532.ZINC.FINGER.RNA.BINDING.PROTEIN. Length = 1052 cysteine-rich intestinal protein [Homo sapiens] >pir G02666 G02666.cysteine-rich protein 1 - human Length = 77	gil 3293537	459	2669	94	94	HLHDQ83
314	840862		gil 1381638	36	353	100	100	HEPAP58
315	840864			407	1096			HTLHY48
316	840936	homologous to Swiss-Prot accession number P16371 [Homo sapiens] >gil 3850562 (AC005944) GRG_HUMAN; ESPI PROTEIN; AMINO ENHANCER OF SPLIT; AES-1/AES-2; gp130 associated protein GAM [Homo sapiens] >pir G01236 G01236.enhancer of split m9/m10 (groucho protein)	gil 435425	3	668	79	79	HOENU32

317	840938	carbonyl reductase [Sus scrofa] >pir JN0703 JN0703 carbonyl reductase (NADPH) (EC 1.1.1.184) - pig >sp Q29529 CBR2_PIG LUNG CARBONYL REDUCTASE [NADPH] (EC 1.1.1.184) (NADPH-DEPENDENT CARBONYL REDUCTASE) (LCR). Length = 244	gnl PID d100 4479	2	745	65	76	HMCA175
318	841884			677	1324			HLQB145
319	842241	(A J009698) embigin protein [Rattus norvegicus] >sp O88775 O88775 EMBIGIN PROTEIN PRECURSOR. Length = 328	gnl PID e1312 986	2	952	60	75	HOFMD52
320	843712			2	202			HSSGR77
321	844040	ribosomal protein L11 [Caenorhabditis elegans] >pir S27795 S27795 ribosomal protein L11 homolog - Caenorhabditis elegans Length = 195	gij I56201	75	500	42	64	HPTGB84
322	844336	(AB009462) LDL receptor related protein 105 [Homo sapiens] >sp O75074 O75074 LDL RECEPTOR RELATED PROTEIN 105. Length = 770	gnl PID d103 3292	831	2285	68	75	HWMFE21
323	844612	collagen binding protein 2 [Homo sapiens] >pir I52968 I52968 colligin-2 - human >sp P50454 CBP2_HUMAN COLLAGEN- BINDING PROTEIN 2 PRECURSOR (COLLIGIN 2). Length = 418	gnl PID d101 2496	528	1466	96	97	HOFME75
324	844617			556	735			HMVCZ36

325	845251	LIV-1 protein [Homo sapiens] >pir G02273 G02273 LIV-1 protein - human >sp Q13433 Q13433 ESTROGEN REGULATED LIV-1 PROTEIN. Length = 752	gi 1256001	23	634	49	67	HBGBB42
326	845764			2	244			HULCF61
327	846187	ATPase alpha subunit (aa 1-1023) [Homo sapiens] >gn P1D1 000505 Na,K-ATPase alpha-subunit [Homo sapiens] >pir A24414 A24414 Na+/K+-exchanging ATPase (EC 3.6.1.37) alpha-1 chain - human >sp P05023 ATN1_HUMAN SODIUM/POTASSIUM- TRANSPORTING ATPASE ALPHA-1 C	gi 28927	151	2403	92	92	HDPLV27
328	HBGDH47R			167	241			IIBGDI147
329	HHENQ86R			2	112			HHENQ86
330	HBGBH23R	(AE000161) bacteriophage lambda endopeptidase homolog [Escherichia coli] >pir B64788 B64788 bacteriophage lambda endopeptidase homolog (EC 3.4.-.-) - Escherichia coli (strain K-12) >sp P75719 ENPP_ECOLI PUTATIVE ENDOPEPTIDASE (EC 3.4.-.-). Length = 153	gi 1786769	1	213	92	92	HBGBH23
331	HANGA53R	(AF013214) acidic ribosomal phosphoprotein PO [Bos taurus] Length = 302	gi 2293577	76	402	80	84	HANGA53

332	HBIMC29R	(AF035959) type-2 phosphatidic acid phosphatase-gamma; phosphatidate phosphohydrolase; phospholipid phosphatase [Homo sapiens] >gi 3025880 (AF056083) phosphatidic acid phosphatase type 2 [Homo sapiens] >gi 2911498 (AF047760) phosphatidic acid phosphohydro (AF061340) F1 ATPase subunit 6 [Artibeus jamaicensis] Length = 226 (AF070447) barrier-to-autointegration factor [Homo sapiens] >sp O75531 O75531 BARRIER-TO-AUTOINTEGRATION FACTOR. Length = 89	gi 3123896	3	317	96	96	HBIMC29
333	HOFAB89R		gi 4164480	86	268	67	82	HOFAB89
334	HAHCP93R		gi 3220255	116	289	69	76	HAHCP93
335	HBGAA76R			14	232			HBGAA76
336	HGBGT12R	A (DNA packaging;641) [Bacteriophage lambda] >pir D04333 JVBPAL DNA- packaging protein A - phage lambda Length = 641	gi 215106	2	349	95	95	HGBGT12
337	HGBBH53R	Actin [Drosophila melanogaster] >pir S14851 S14851 actin - fruit fly (Drosophila melanogaster), >sp Q24228 Q24228 ACTIN. Length = 100	gi 7550	2	445	93	97	HGBBH53

338	HTXPI29R	aldolase A (EC 4.1.3.13) [Homo sapiens] >gi 28597 aldolase A (AA 1-364) [Homo sapiens] >pir S14084 ADHUA fructose-bisphosphate aldolase (EC 4.1.2.13) A - human >sp P04075 ALFA_HUMAN FRUCTOSE-BISPHOSPHATE ALDOLASE A (EC 4.1.2.13) (MUSCLE-TYPE ALDOLASE). {S}	gi 178351	1	453	86	86	HTXPI29
339	HOFMG33R	ATPase [Equus caballus] >sp P48662 ATP6_HORSE ATP SYNTHASE A CHAIN (EC 3.6.1.34) (PROTEIN 6). Length = 226	gi 577577	28	309	57	62	HOFMG33
340	HCGAC11R			1	345			HCGAC11
341	HCIAC54R			37	168			HCIAC54
342	HBGAA54R			1	282			HBGAA54
343	HAOMC34R	calpactin I heavy chain (p36) [Bos taurus] >pir A03081 LUBO36 annexin II - bovine >sp P04272 ANX2_BOVIN ANNEXIN II (LIPOCORTIN II) (CALPACTIN I HEAVY CHAIN) (CHROMOBINDIN 8) (P36) (PROTEIN I) (PLACENTAL ANTICOAGULANT PROTEIN IV) (PAP-IV). {SUB 2-339} Leng	gi 162779	2	115	73	80	HAOMC34
344	H2LAU88R	copine I [Homo sapiens] >sp Q99829 Q99829 COPINE I. Length = 537	gi 1791257	1	576	95	95	H2LAU88
345	HDPJR77R	DNA topoisomerase II [Homo sapiens] >gi 38325 DNA topoisomerase II [Homo sapiens] {SUB 448-681} Length = 1031	gi 288565	3	311	100	100	HDPJR77

346	HTTIO41R	docking protein [Homo sapiens] >pir A29440 A29440 signal recognition particle receptor - human Length = 638	gi 30866	90	404	94	95	HTTIO41
347	H2CBU29R	electron transport flavoprotein [Homo sapiens] >pir A31998 A31998 electron transfer flavoprotein alpha chain precursor - human >sp P13804 ETFA_HUMAN ELECTRON TRANSFER FLAVOPROTEIN ALPHA-SUBUNIT PRECURSOR (ALPHA-ETF) >gnl PID e1331769 (AJ224002) electron	gi 182251	2	442	100	100	H2CBU29
348	HBMVA11R	GARS protein [Homo sapiens] >sp Q15374 Q15374 GARS PROTEIN. Length = 433	gnl PID d100 7383	1	108	81	84	HBMVA11
349	HDPUL86R	GC kinase [Homo sapiens] >pir A53714 A53714 protein kinase (EC 2.7.1.37) BL44 - human >sp Q12851 Q12851 GC KINASE. Length = 819	gi 531820	3	317	64	65	HDPUL86
350	HTXNT16R	GTP-binding protein [Homo sapiens] >gi 577779 GTP-binding protein [Homo sapiens] >pir A55014 A55014 GTP-binding protein - human >sp P55039 DRG2_HUMAN DEVELOPMENTALLY REGULATED GTP-BINDING PROTEIN DRG2. Length = 364	gi 577779	2	463	100	100	HTXNT16
351	HBGAA13R	H (tail component;853) [Bacteriophage lambda] >pir G43008 TLBPHL minor tail protein precursor H - phage lambda Length = 853	gi 215120	1	267	97	97	HBGAA13

352	HLXNA54R	heat shock protein HSP27 [Homo sapiens] >gi 433598 28 kDa heat shock protein [Homo sapiens] >gi 1913885 heat shock protein [Homo sapiens] >pir S12102 HHHU27 heat shock protein 27 - human >sp G248440 G248440 28 KDA HEAT SHOCK PROTEIN HOMOLOG FRAGMENT 2. {S	gi 32478	2	256	98	98	HLXNA54
353	HCHOH37R	Hep27 protein [Homo sapiens] >pir S66665 S66665 nuclear protein Hep27 - human >sp Q13268 HE27_HUMAN HEP27 PROTEIN (PROTEIN D). {SUB 24-280} Length = 280	gi 1079566	337	564	75	81	HCHOH37
354	H2LAX93R	histone H2B [Gallus gallus] >gi 63434 histone H2B [Gallus gallus] >gi 63452 histone H2B (AA 1 - 126) [Gallus gallus] >gi 63456 histone H2B (AA 1 - 126) [Gallus gallus] >gi 63458 histone H2B [Gallus gallus] >gi 63460 histone H2B (AA 1 - 126) [Gallus gallus] homologue to elongation factor 1-gamma from A.salina [Homo sapiens] >gi 31104 elongation factor-1-gamma [Homo sapiens] >pir S22655 S22655 translation elongation factor eEF-1 gamma chain - human >sp P26641 EF1G_HUMAN ELONGATION FACTOR 1-GAMMA (EF- 1-GAMMA).	gi 211845	191	505	89	96	H2LAX93
355	HWAFFW10R		gi 31102	3	434	98	98	HWAFFW10

356	HBNAB19R	human complement C1r [Homo sapiens] >pir A24170 C1HURB complement subcomponent C1r (EC 3.4.21.41) precursor - human >sp P00736 C1R_HUMAN COMPLEMENT C1R COMPONENT PRECURSOR (EC 3.4.21.41). Length = 705	gil179644	2	193	98	98	HBNAB19
357	HBGDD17R	hypothetical protein [Escherichia coli] >gil1786774 (AE000161)orf, hypothetical protein [Escherichia coli] >pir G64788 G64788 hypothetical protein b0561 - Escherichia coli (strain K-12) Length = 247	gil1778474	1	207	98	98	HBGDD17
358	HBIAB72R	hypoxanthine phosphoribosyltransferase [Sus scrofa] >sp P79306 P79306 HYPOXANTHINE PHOSPHORIBOSYLTRANSFERASE (FRAGMENT). Length = 85	gnl PID e2919 69	2	169	81	86	HBIAB72
359	HFIIEH41R	interferon-gamma induced protein [Homo sapiens] >pir I54501 I54501 interferon gamma-induced protein IFI 16 - human >sp Q16666 IFI16_HUMAN GAMMA- INTERFERON-INDUCIBLE PROTEIN IFI-16 (INTERFERON-INDUCIBLE MYELOID DIFFERENTIATION TRANSSCRIPTIONAL ACTIVATOR). Le	gil184569	5	406	96	97	HFIIEH41
360	H2CBB43R	J (tail:host specificity;1132) [Bacteriophage lambda] >pir D43009 QSBPL host specificity protein J - phage lambda Length = 1132	gil215125	2	400	99	99	H2CBB43

361	H2CBQ77R	J (tail:host specificity; 1132) [Bacteriophage lambda] >pir D43009 QSBPL host specificity protein J - phage lambda Length = 1132	3	272	97	97	H2CBQ77
362	HATAO24R	J (tail:host specificity; 1132) [Bacteriophage lambda] >pir D43009 QSBPL host specificity protein J - phage lambda Length = 1132	2	247	71	71	HATAO24
363	HOEMK06R	K (tail component; 199) [Bacteriophage lambda] >pir H43009 TJBPKL tail assembly protein K - phage lambda Length = 199	3	149	97	97	HOEMK06
364	HADCH03R	mitochondrial acetoacetyl-CoA thiolase precursor [Homo sapiens] Length = 427	2	256	83	83	HADCH03
365	HCHAG30R	Mta1 [Rattus norvegicus] >pir A54766 A54766 metastasis-associated protein mta-1 - rat >sp Q62599 MTA1_RAT METASTASIS-ASSOCIATED PROTEIN MTA1. Length = 703	2	271	92	92	HCHAG30
366	HOFAD96R	NADH dehydrogenase subunit 4L [Felis catus] >sp P48931 NULM_FELCA NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 4L (EC 1.6.5.3). Length = 98	2	253	50	52	HOFAD96
367	H2CBX07R	Nin 221 (pept unknown; 221) [Bacteriophage lambda] >pir G43011 Q1BP1L multiple specificity phosphoprotein phosphatase (EC 3.1.3.-) - phage lambda >sp P03772 PP_LAMBD SERINE/THREONINE PROTEIN PHOSPHATASE (EC 3.1.3.16). Length = 221	2	184	100	100	H2CBX07

368	HDPLN02R	nuclear corepressor KAP-1 [Homo sapiens] Length = 835	gi 1699027	149	454	90	90	HDPLN02
369	HT4FU27R	nuclear corepressor KAP-1 [Homo sapiens] Length = 835	gi 1699027	96	287	95	95	HT4FU27
370	HAEAI26R	open reading frame A; putative [Homo sapiens] Length = 84	gi 190369	109	291	78	80	HAEAI26
371	HCDAR56R	p23 [Homo sapiens] >pir A56211 A56211 progesterone receptor-related protein p23 - human >sp Q15185 Q15185 (P23). Length = 160	gi 438652	2	208	90	92	HCDAR56
372	HCDCW35R	precursor [Homo sapiens] Length = 631	gi 36049	3	155	78	84	HCDCW35
373	H2CBN76R	proteasome subunit C5 [Homo sapiens] >gn PID e 1334433 (AL031259) C5 (proteasome subunit HC5) [Homo sapiens] >pir S15973 SNHUC5 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C5 - human >sp P20618 PRC5_HUMAN PROTEASOME COMPONENT C5 (EC 3.4.99.4	gn PID d 100 1116	3	464	99	99	H2CBN76
374	HAGFX49R	proteasome subunit C5 [Homo sapiens] >gn PID e 1334433 (AL031259) C5 (proteasome subunit HC5) [Homo sapiens] >pir S15973 SNHUC5 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C5 - human >sp P20618 PRC5_HUMAN PROTEASOME COMPONENT C5 (EC 3.4.99.4	gn PID d 100 1116	1	288	98	100	HAGFX49

375	HNEEG64R	put. major coat protein (AA 1-341) [Bacteriophage phi-80] >pir S03314 VHBP80 major capsid protein - phage phi-80 >sp P05481 HEAD_BPPH8 MAJOR HEAD PROTEIN (GPE)(GP5) (MAJOR COAT PROTEIN). Length = 341	gil 5769	17	232	81	97	HNEEG64
376	HTXKR32R	putative nucleotide-binding protein [Homo sapiens] >pir JC4010 JC4010 nucleotide-binding protein - human >sp P53384 NBP_HUMAN NUCLEOTIDE-BINDING PROTEIN (NBP). Length = 320	gil 5644	3	374	100	100	HTXKR32
377	HAIBZ58R	putative start codon [Homo sapiens] Length = 210	gil 895845	2	433	65	65	HAIBZ58
378	H6EAF46R	rex (exclusion;279) [Bacteriophage lambda] >gil 5068 reading frame (rex) protein [Bacteriophage 434] >pir E43010 IMBPAL rexA protein - phage lambda Length = 279	gil 215146	43	333	92	93	H6EAF46
379	H2LA W60R	ribosomal protein L27a [Homo sapiens] >pir S55914 S55914 ribosomal protein L27a - human Length = 148	gil 550017	3	545	88	88	H2LA W60
380	H2LAK40R	ribosomal protein L31 [Sus scrofa] >gil 36130 ribosomal protein L31 (AA 1-125) [Homo sapiens] >gil 57115 ribosomal protein L31 (AA 1-125) [Rattus norvegicus] >pir S05576 R5HU31 ribosomal protein L31 - human >pir A26417 R5RT31 ribosomal protein L31 - rat >gn	gnl PID e2764 36	76	483	77	80	H2LAK40

381	H2LAY71R	ribosomal protein L35 [Homo sapiens] >pir G01477 G01477 ribosomal protein L35 - human Length = 123	gil562074	70	495	100	100	H2LAY71
382	HCHAH62R	ribosomal protein L8 [Homo sapiens] >gil57704 ribosomal protein L8 [Rattus rattus] >gil1527178 ribosomal protein L8 [Mus musculus] >pir J0177 R5RTL8 ribosomal protein L8, cytosolic - rat >pir JN0923 JN0923 ribosomal protein L8, cytosolic - human >gil3851	gil433899	1	222	76	76	HCHAH62
383	H6EEF31R	ribosomal protein S2 [Rattus norvegicus] >sp O55211 O55211 RIBOSOMAL PROTEIN S2. Length = 257	gil2920825	1	300	89	91	H6EEF31
384	HDPBT55R	RNAse L inhibitor [Mus musculus] >sp O88793 O88793 RNAse L INHIBITOR. Length = 599	gil3273417	71	127	81	86	HDPBT55
385	HASAW80R	S.macroura Wilms tumour protein [Sminthopsis macroura] Length = 239	gil987118	1	162	90	98	HASAW80
386	HCHAF25R	SSR alpha subunit [Homo sapiens] >pir I38246 I38246 SSR alpha subunit - human Length = 286	gil551638	2	421	95	95	HCHAF25
387	HLTHH84R	UMP synthase [Homo sapiens] >pir A30148 A30148 UMP synthase - human Length = 480	gil340168	2	391	99	99	HLTHH84
388	H2CBU20R			39-	143			H2CBU20
389	HADAA62R			3	218			HADAA62
390	HADDC09R			16	174			HADDC09
391	HAIAB75R			2	211			HAIAB75

392	HAMGA37R	3	119	HAMGA37
393	HAQA110R	1	81	HAQA110
394	HBFMEE95R	3	218	HBFMEE95
395	HBGBH24R	1	81	HBGBH24
396	HBGBT78R	1	69	HBGBT78
397	HBGCB06R	3	140	HBGCB06
398	HBGDO01R	1	156	HBGDO01
399	HBIBJ73R	3	341	HBIBJ73
400	HBJLE85R	3	398	HBJLE85
401	HBNAD53R	2	187	HBNAD53
402	HBNAT63R	54	173	HBNAT63
403	HCE4H65R	2	193	HCE4H65
404	HCFLJ44R	92	274	HCFLJ44
405	HCHMW05R	3	221	HCHMW05
406	HCHNR50R	2	103	HCHNR50
407	HE8DS01R	2	64	HE8DS01
408	HFEBP31R	109	276	HFEBP31

409	HLDXE36R	6	167	HLDXE36
410	HLTGV28R	181	414	HLTGV28
411	HODFW25R	42	308	HODFW25
412	HOEMQ91R	1	129	HOEMQ91
413	HOGBG56R	57	386	HOGBG56
414	HOSMT44R	2	151	HOSMT44
415	HRAEE04R	51	191	HRAEE04
416	HULFN65R	3	272	HULFN65
417	HWLVW23R	1	153	HWLVW23
418	HWLWE77R	149	289	HWLWE77

The first column of Table 1 shows the "SEQ ID NO:" for each of the 418 breast/ovarian cancer antigen polynucleotide sequences of the invention.

The second column in Table 1, provides a unique "Sequence/Contig ID" identification for each breast, ovarian, breast cancer and/or ovarian cancer associated sequence. The third column in Table 1, "Gene Name," provides a putative identification of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database, such as GenBank (NCBI). The great majority of the cDNA sequences reported in Table 1 are unrelated to any sequences previously described in the literature. The fourth column, in Table 1, "Overlap," provides the database accession no. for the database sequence having similarity. The fifth and sixth columns in Table 1 provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as SEQ ID NO:Y. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated by the nucleotide position nos. "Start" and "End". Also provided are polynucleotides encoding such proteins and the complementary strand thereto. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity) observed between the aligned sequence segments of the translation product of SEQ ID NO:X and the database sequence.

The ninth column of Table 1 provides a unique "Clone ID" for a clone related to each contig sequence. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO:X was determined by directly sequencing the referenced clone. The reference clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases, however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length cDNA can be obtained by methods described elsewhere herein.

Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, or more of any one or more of these public ESTs are optionally excluded from the invention.

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing as SEQ ID NO:1 through SEQ ID NO:418) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing as SEQ

ID NO:418 through SEQ ID NO:836) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X has uses including, but not limited to, in designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the related cDNA clone
5 contained in a library deposited with the ATCC. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y have uses that include, but are not limited to, generating antibodies which
10 bind specifically to the breast/ovarian cancer antigen polypeptides, or fragments thereof, and/or to the breast/ovarian cancer antigen polypeptides encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions
15 of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over
20 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing the related cDNA clone
25 (deposited with the ATCC, as set forth in Table 1). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X.

The predicted amino acid sequence can then be verified from such deposits.
30 Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to vectors or plasmids which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC on:

5 **Table 2**

ATCC Deposits	Deposit Date	ATCC Designation Number
LP01, LP02, LP03, LP04, LP05, LP06, LP07, LP08, LP09, LP10, LP11,	May-20-97	209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069
LP12	Jan-12-98	209579
LP13	Jan-12-98	209578
LP14	Jul-16-98	203067
LP15	Jul-16-98	203068
LP16	Feb-1-99	203609
LP17	Feb-1-99	203610
LP20	Nov-17-98	203485
LP21	Jun-18-99	PTA-252
LP22	Jun-18-99	PTA-253
LP23	Dec-22-99	PTA-1081

each is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as shown in Table 5. These deposits are referred to as
10 “the deposits” herein. The tissues from which the clones were derived are listed in Table 5, and the vector in which the cDNA is contained is also indicated in Table 5. The deposited material includes the cDNA clones which were partially sequenced and are related to the SEQ ID NO:X described in Table 1 (column 9). Thus, a clone which is isolatable from the ATCC Deposits by use of a sequence listed as SEQ ID NO:X may include the entire coding
15 region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Although the sequence listing lists only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to complete the sequence of the DNA included in a clone isolatable from the

ATCC Deposits by use of a sequence (or portion thereof) listed in Table 1 by procedures hereinafter further described, and others apparent to those skilled in the art.

Also provided in Table 5 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res.* 16:7583-7600 (1988); Altling-Mees, M. A. and Short, J. M., *Nucleic Acids Res.* 17:9494 (1989)) and pBK (Altling-Mees, M. A. et al., *Strategies* 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

Vectors pSport1, pCMVSPORT 1.0, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus* 15:59 (1993). Vector lacmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in a deposited cDNA clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in the related cDNA clone in the deposit, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the related cDNA clone (See, e.g., columns 1 and 9 of Table 1). The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the the dDNA in the related cDNA clone contained in a deposited library, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the related cDNA clone contained in a deposited library.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would unduly burden the disclosure of this application. Accordingly, for each "Contig Id" listed in the first column of Table 3, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described in the second column of Table 3 by the general formula of a-b, each of which are uniquely defined for the SEQ ID NO:X corresponding to that Contig Id in Table 1. Additionally, specific embodiments are directed to polynucleotide sequences excluding at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. for each Contig Id which may be

included in column 3 of Table 3. In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example.

Table 3

Sequence/ Contig ID	General formula	Genbank Accession No.
419266	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1899 of SEQ ID NO:1, b is an integer of 15 to 1913, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:1, and where b is greater than or equal to a + 14.	T68585, T68665, T86313, T86314, R12356, R31374, R32873, R37282, R84617, R85369, R99171, H48474, N23871, N58201, N74557, W90334, AA031318, AA031427, AA130231, AA256587
429114	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1411 of SEQ ID NO:2, b is an integer of 15 to 1425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:2, and where b is greater than or equal to a + 14.	R20542, R42676, R42676, R20542, R61501, H08662, H77556, H97365, N24198, N33135, N74546, N93573, W02941, W52194, AA004624, AA004721, AA046710, AA235395, AA235479
506777	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 340 of SEQ ID NO:3, b is an integer of 15 to 354, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:3, and where b is greater than or equal to a + 14.	
508678	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 500 of SEQ ID NO:4, b is an integer of 15 to 514, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:4, and where b is greater than or equal to a + 14.	W37175, AA121532, AA127694
508968	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T71941, T94428, T94514, H02313, N26913, N47870, N66244, N92418, W31301, W42459, W42564, AA084031, AA126786, AA258050, AA459772

	formula of a-b, where a is any integer between 1 to 2021 of SEQ ID NO:5, b is an integer of 15 to 2035, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:5, and where b is greater than or equal to a + 14.	
509029	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1182 of SEQ ID NO:6, b is an integer of 15 to 1196, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:6, and where b is greater than or equal to a + 14.	R11213, R11271, H14072, H14071, H51531, H66637, H66636, W23707, W35307, AA025586, AA025710, AA058796, AA113917
519726	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 610 of SEQ ID NO:7, b is an integer of 15 to 624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:7, and where b is greater than or equal to a + 14.	AA236015, AA236085, AA256106
522632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 287 of SEQ ID NO:8, b is an integer of 15 to 301, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:8, and where b is greater than or equal to a + 14.	
524655	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 672 of SEQ ID NO:9, b is an integer of 15 to 686, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:9, and where b is greater than or equal to a + 14.	T66495, R15869, R39696, H16266, H20784, H22599, N68150, W58001, W57856
525847	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 383 of SEQ ID NO:10, b is an integer of 15 to 397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:10, and where b is greater than or equal to a + 14.	
530306	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 549 of SEQ ID NO:11, b is an integer of 15 to 563, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.	
532818	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 429 of SEQ ID NO:12, b is an integer of 15 to 443, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.	AA188990, AA191040
533385	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2424 of SEQ ID NO:13, b is an integer of 15 to 2438, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.	
533532	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2333 of SEQ ID NO:14, b is an integer of 15 to 2347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	T94240, T77619, R13236, R17515, R33142, R33294, R39249, R40318, R42609, R42609, R40318, R75952, H03594, H12337, H12391, H70913, H70916, H70996, H71001, H87858, H70913, N21374, N31326, N35068, N35435, N43807, N45045, W46431, W46486, W51917, AA019546, AA018858, AA056764, AA056767, AA058441, AA058445, AA083228, AA083269, AA115939, AA122236, AA147307, AA159802,

	NO:14. and where b is greater than or equal to a + 14.	AA165015. AA165642. AA181869, AA186834, AA252269. AA255892. AA463239, AA463240
534852	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1992 of SEQ ID NO:15, b is an integer of 15 to 2006, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15. and where b is greater than or equal to a + 14.	T55469, T63434. R10603. R10604, H50597, H92640, H94634. W39162, W93243, W94634, W94719, N90240. AA053667, AA167312, AA253414. AA253389
537910	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 972 of SEQ ID NO:16, b is an integer of 15 to 986, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.	R23785
538460	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1575 of SEQ ID NO:17, b is an integer of 15 to 1589, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.	R13084. R40514, R40514, R55303, R55402, W67446
539577	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 832 of SEQ ID NO:18, b is an integer of 15 to 846, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.	T49208, N35488, AA088419, AA127572, AA127649, AA156316, AA169250
548379	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2178 of SEQ ID NO:19, b	R23778, H70824

	is an integer of 15 to 2192, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.	
548489	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 997 of SEQ ID NO:20, b is an integer of 15 to 1011, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.	T49861, T49862, T56225, T56367, T72170, T72948, T92867, T74728, R08625, R08719, R17408, R24674, R25174, R25378, R25997, R26800, R28401, R31330, R31589, R42642, R45259, R42642, R45259, R62552, R62553, R66386, R67726, R68781, R68878, H25120, H25121, H41115, H41190, H41191, R84227, R87629, H53386, H64419, H64476, H72640, H72641, H64419, H99301, N22341, N25846, N29370, N29843, N47918, N57261, N59763, N63813, N94171, W23786, W45524, W72111, W77797, AA010718, AA011164, AA033553, AA033554, AA062727, AA062741, AA062784, AA069811, AA075470, AA075471, AA081844, AA083492, AA084442, AA100358, AA126263, AA126354, AA136544, AA136648, AA146862, AA146863, AA179509, AA179540, AA179775, AA180492, AA181719, AA188903, AA189140, AA226959, AA227247
548595	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2005 of SEQ ID NO:21, b is an integer of 15 to 2019, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.	T61537, T69836, R10679, R42501, R46798, R42501, R46798, H05289, H05822, H12239, H16816, H40312, R86905, R86985, N21432, N73268, W73102, N91565, AA033533, AA053026, AA121547, AA127684, AA190356, AA195451, AA226965, AA232522, AA258142
549337	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2008 of SEQ ID NO:22, b is an integer of 15 to 2022, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.	
549777	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1112 of SEQ ID NO:23, b	T81557, R27931, R38730, R39493, R39494, R66845, R67942, R69099, R69214, R69613, R69703, R69740, R72430, R72478, R73090, R73091, R73872, R73955, R82662, R82715, H01096, H01097, H72113, N76139, W58493, W72884, W74409, W94644, W92532,

	is an integer of 15 to 1126, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.	AA022916, AA022917, AA039661, AA039660, AA043439, AA054965, AA152376, AA148360, AA181225, AA188435
553091	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2584 of SEQ ID NO:24, b is an integer of 15 to 2598, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.	
553827	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 397 of SEQ ID NO:25, b is an integer of 15 to 411, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.	
556350	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:26, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.	T70920, R01856, R37402, H21077, H21531, R94734, N29364, N32255, N80553, W07675, W58340, W58661, W67208, W67352, AA039658, AA039659, AA046392, AA055650, AA058365, AA070442, AA088882, AA102056, AA134144, AA165363, AA171617, AA173761, AA173771, AA252260, AA464575, AA464679
556351	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1889 of SEQ ID NO:27, b is an integer of 15 to 1903, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.	T70981, R01855, R13494, H21076, H24431, H24460, R94817, N47912, AA040086, AA040133, AA055706, AA056162, AA058484, AA102055, AA102304, AA130304, AA173608, AA195879
557007	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	H13846, H13894, H16354, H20742, H20743, R97935, R97936, H87445, N29633, AA015991, AA045671, AA045670, AA099154, AA099252

	sequence described by the general formula of a-b, where a is any integer between 1 to 1319 of SEQ ID NO:28, b is an integer of 15 to 1333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.	
558140	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1313 of SEQ ID NO:29, b is an integer of 15 to 1327, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.	T62991, W58535, W58500, AA053629, AA083878, AA112892, AA157250, AA157345, AA194089, AA253436, AA250750
558456	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 695 of SEQ ID NO:30, b is an integer of 15 to 709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.	
558708	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1094 of SEQ ID NO:31, b is an integer of 15 to 1108, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.	R38385, W24640, W48793, W49619
574789	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 512 of SEQ ID NO:32, b is an integer of 15 to 526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.	N49156

578203	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 541 of SEQ ID NO:33, b is an integer of 15 to 555, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.	AA149853
585385	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 333 of SEQ ID NO:34, b is an integer of 15 to 347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.	
588869	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 736 of SEQ ID NO:35, b is an integer of 15 to 750, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.	
597076	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1277 of SEQ ID NO:36, b is an integer of 15 to 1291, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.	
598656	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1521 of SEQ ID NO:37, b is an integer of 15 to 1535, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.	
611880	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 281 of SEQ ID NO:38, b is an integer of 15 to 295, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.	
614329	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1286 of SEQ ID NO:39, b is an integer of 15 to 1300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.	T49777, T51334, T49778, T66835, T66836, T78401, R33579, R33684, R34361, R34476, R72556, R75702, H01591, H02719, H13232, H13599, H13942, H13943, H63376, H80729, H80730, H89353, H89539, H99395, N26995, N32930, N40116, N42081, N50408, N50460, N63978, N67308, N92847, W46413, AA126994, AA128141, AA146958, AA146957, AA425764
616066	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 201 of SEQ ID NO:40, b is an integer of 15 to 215, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.	
620956	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 460 of SEQ ID NO:41, b is an integer of 15 to 474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.	
621889	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 411 of SEQ ID NO:42, b is an integer of 15 to 425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.	
624017	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1173 of SEQ ID NO:43, b is an integer of 15 to 1187, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.	T61010, AA071044, AA088260, AA098798, AA102017, AA100707, AA111883, AA113305, AA121495, AA133235, AA131438, AA132011, AA132866, AA143457, AA146581, AA146805, AA146928, AA155613, AA155609, AA158090, AA158263, AA164694, AA165591, AA176429, AA226820
651784	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 501 of SEQ ID NO:44, b is an integer of 15 to 515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.	W32583, W68240, W94174, AA251670, AA252011, AA252266, AA425209
651826	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1485 of SEQ ID NO:45, b is an integer of 15 to 1499, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.	T47384, T47385, T60137, T60194, T71947, T95050, T95146, R25340, R25476, R26117, R26301, R27566, R27664, R28180, R33393, R35872, R35873, R36483, R48329, R48438, R62139, R62244, R66007, R66008, R66764, R70718, R70719, R73674, R73761, R74132, R76569, R76643, R77265, R77312, R78827, R79686, R79687, R81316, R81751, H00804, H00891, H01415, H01416, H02522, H03673, H13925, H13926, H24743, H26369, H26727, H26728, H27132, H27480, H27663, H28192, H28235, H41929, H41977, H42604, H43209, H43258, H45278, H45348, H53585, H53906, H61785, H61786, H78337, H78338, H87337, H87871, H95183, N27090, N27092, N40499, N40502, N99158, W24165, W60193, AA039817, AA041344, AA074512, AA079058, AA079156, AA079157, AA085829, AA085974, AA100095, AA113304, AA142843, AA149898, AA156331, AA157820, AA157895, AA158552, AA159177, AA176093, AA179607, AA179608, AA176333, AA187637, AA186769, AA188622, AA188742, AA188975
653282	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 379 of SEQ ID NO:46, b is an integer of 15 to 393, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.	
657122	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 224 of SEQ ID NO:47, b is an integer of 15 to 238, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.	
661442	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 925 of SEQ ID NO:48, b is an integer of 15 to 939, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.	R18101, AA424721
664914	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1757 of SEQ ID NO:49, b is an integer of 15 to 1771, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.	T86944, T87027, R11421, T81153, T81380, R17243, R17453, R19171, R27826, R27927, R35295, R35940, R41854, R42800, R48191, R48192, R49457, R51209, R52247, R53413, R41854, R42800, R49457, R55257, R55475, R59472, R71390, R81811, R81915, H05137, H07974, H30702, H42552, H57923, H58015, N71127, N74282, N75329, N93224, W01557, W04382, W04780, W23438, W35253, W38865, AA176204, AA194869, AA199875, AA251414
666654	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 383 of SEQ ID NO:50, b is an integer of 15 to 397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:50, and where b is greater than or equal to a + 14.	
667084	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1621 of SEQ ID NO:51, b is an integer of 15 to 1635, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.	R71869, R71870, H22387, H27160, H46592, H61204, H62108, N25274, N94410, AA026642, AA069188, AA069189, AA076423, AA076388, AA076533, AA076540, AA122346, AA121039, AA121092, AA133121, AA143471, AA143470, AA143728, AA156363, AA156404, AA158498, AA159190, AA159201, AA159286, AA160335, AA159837, AA159573, AA160367, AA159548, AA160456, AA160697, AA160789, AA179329, AA181540, AA182669, AA186881, AA186887, AA188535, AA188540, AA190669, AA190973, AA191557, AA235457, AA458511, AA418203
667380	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1766 of SEQ ID NO:52, b is an integer of 15 to 1780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.	T87574, R10276, R10277, T79847, R49790, R49832, R59538, R59539, R86940, R87067, R87722, R98577, R98578, R99022, R99795, H72692, H93036, H93942, H93941, N54059, N62326, N64719, N66726, N73888, N74171, N91734, N93505, W02054, W03949, W04337, W21317, AA192562, AA192563, AA223984, AA224049
669530	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 476 of SEQ ID NO:53, b is an integer of 15 to 490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.	T49160, T49161, H41659, R88196, W60799, W60930, AA046915, AA046972, AA069703, AA464334
671315	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1930 of SEQ ID NO:54, b is an integer of 15 to 1944, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.	
671993	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 980 of SEQ ID NO:55, b is an integer of 15 to 994, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.	
674618	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 314 of SEQ ID NO:56, b is an integer of 15 to 328, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.	
675027	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1475 of SEQ ID NO:57, b is an integer of 15 to 1489, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.	T86474, AA133454, AA203346
677202	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1269 of SEQ ID NO:58, b is an integer of 15 to 1283, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.	T47486, T47487, T47666, T50413, T50493, T50519, T51852, T53234, T57067, T60776, T40856, T93579, T94432, T94435, T96391, R43542, R43542, H21618, H73240, H88867, H88868, H89122, H88868, H89122, N21997, N22243, N22815, N45720, N48998, N52063, N59239, N62103, N66419, N66708, N66782, N67139, N67283, N67447, N68047, N70159, N71198, N74676, N76707, N78333, N80016, N92971, N93518, W05738, W45694, W48845, W80602, AA057801, AA063330, AA064827, AA065165, AA065178, AA065179, AA069552, AA070491, AA070949, AA070969, AA071333, AA071358, AA074331, AA081280, AA111928, AA112051, AA132018, AA132121, AA147357, AA157065, AA157085, AA157890, AA160054, AA181729, AA182765, AA187698, AA186444, AA196168, AA196244, AA224187
678504	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 726 of SEQ ID NO:59, b is	

	an integer of 15 to 740, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.	
678985	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1277 of SEQ ID NO:60, b is an integer of 15 to 1291, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.	
682161	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 957 of SEQ ID NO:61, b is an integer of 15 to 971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.	
683476	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 604 of SEQ ID NO:62, b is an integer of 15 to 618, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.	
691146	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1124 of SEQ ID NO:63, b is an integer of 15 to 1138, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.	T48865, T48866, T48901, T47562, T48902, T54258, T54365, T69783, T70768, R08012, R09058, R09059, T83437, T84082, T99021, R09059, R19174, R21551, R22562, R28286, R48757, R48758, R49683, R49683, R62406, R62407, R70222, R75607, R77000, R78400, R78401, R80802, H02840, H03734, H24549, H26291, H26447, H27912, H43630, H47817, R83903, R83904, R94147, H49533, H49773, H50716, H50820, H87446, H87553, H93471, H93472, H98814, N22867, N32137, N32762, N34334, N35009, N36932, N43763, N46205, N52251, N56805, N72290, N95794, W02713, W02886, W17176, W24905, W25571, W25688,

		W67795, W72687, W72962, W77793, W79704, W81376, W86301, W86316, AA025519, AA025959, AA026653, AA029556, AA029704, AA079472, AA121306, AA136679, AA148681, AA148680, AA181745, AA425923
693589	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 404 of SEQ ID NO:64, b is an integer of 15 to 418, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.	
694991	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2822 of SEQ ID NO:65, b is an integer of 15 to 2836, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.	
698303	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2291 of SEQ ID NO:66, b is an integer of 15 to 2305, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.	T83582, T84417, T85606, R66380, R67111, R76298, H96019, H96020, N25659, N25661, N34260, N34263, N70618, W05500, W15421, W23670, W39659, AA015855, AA033569, AA033570, AA044566, AA044583, AA178933, AA179025
698669	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1893 of SEQ ID NO:67, b is an integer of 15 to 1907, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.	T47115, T47116, R48786, R48893, R55495, R71847, R78934, R79033, R82776, H26587, H27077, R97760, H59232, H79115, H79116, N22948, N23658, N26858, N28757, N39967, N71599, W24648, W60157, W67490, W67491, W67815, W72921, W94215, AA009634, AA026899, AA026900, AA029244, AA029040, AA031846, AA031847, AA032073, AA034285, AA034992, AA036865, AA037006, AA040908, AA039990, AA040521, AA040522, AA040773, AA043726, AA044071, AA044182, AA042948, AA043067, AA046606, AA046721, AA062914, AA074334, AA076039, AA076203, AA079763, AA079764, AA082550, AA085926, AA099318,

		AA099836, AA102385, AA101039, AA101040, AA112571, AA112572, AA114828, AA114951, AA128001, AA128082, AA126986, AA128134, AA128459, AA129910, AA131403, AA131503, AA147437, AA147438, AA150961, AA151051, AA156785, AA156855, AA157912, AA157913, AA158544, AA158545, AA158554, AA158553, AA211822, AA460840, AA461144
705696	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 801 of SEQ ID NO:68, b is an integer of 15 to 815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.	H20141, H20156, H20236, H20250, H49965, H50007, H50487, W92252, AA045116, AA134141, AA142968
706393	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1136 of SEQ ID NO:69, b is an integer of 15 to 1150, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.	T48975, T51242, T51357, T59673, T59807, T62725, T62875, T72330, T97577, R01168, R21893, R22365, R35745, R41863, R41863, R63676, R65881, R72862, R73334, R75659, R75767, H02871, H03430, H03512, H14924, H23660, H30020, H30277, H39675, H40069, H40278, H40526, H41667, H41700, H43170, H43670, H45130, H45172, H45173, H45433, H46542, H46952, H46953, H62390, H78695, H78777, H84781, H85405, H92309, N20534, N33402, N38945, N57790, N57945, N59752, W94488, W94489, AA044423, AA043057, AA081370, AA081371, AA099447, AA112623, AA112622, AA143199, AA143214, AA149467, AA149553, AA157049, AA157201, AA157952, AA157953, AA158049, AA158435, AA158837, AA158841, AA161074, AA161078, AA180395, AA251447, AA419021, AA428783, AA429093
707357	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 330 of SEQ ID NO:70, b is an integer of 15 to 344, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.	
707360	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	

	formula of a-b, where a is any integer between 1 to 434 of SEQ ID NO:71, b is an integer of 15 to 448, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.	
707375	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2811 of SEQ ID NO:72, b is an integer of 15 to 2825, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.	T54138, T65139, T65330, T80324, T83140, R00512, R00612, R19513, R31469, R31470, R47795, R77921, R78022, R80012, H02327, H02429, H06404, H06405, H08607, H08608, H14264, H18370, H19266, H19267, H21399, H21471, H47094, H47185, R85467, R87496, R87501, R87581, R88189, R88226, R88227, N23376, N32357, N58463, N66212, N93661, N99103, W19083, W24383, W68601, W68602, W68723, W68745, AA016149, AA040296, AA056973, AA135439, AA135519, AA135580, AA135856, AA158858, AA161122, AA226730, AA226764, AA227471, AA227481, AA232259
707754	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 496 of SEQ ID NO:73, b is an integer of 15 to 510, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.	
711172	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 444 of SEQ ID NO:74, b is an integer of 15 to 458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.	
712248	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 363 of SEQ ID NO:75, b is an integer of 15 to 377, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or	

	equal to $a + 14$.	
715445	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 2056 of SEQ ID NO:76, b is an integer of 15 to 2070, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to $a + 14$.	T88778, T97557, T97604, R17189, R27615, R30849, R41740, R48616, R41740, H12351, R93768, R98882, R98972, H59983, N23156, N32736, N34539, N55086, N62785, N67224, N77297, N78823, N79734, W07252, W90651, AA037793, AA037794, AA055196, AA055286, AA113425, AA233917, AA234165, AA258602, AA258548, AA426581, AA429080
716362	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 983 of SEQ ID NO:77, b is an integer of 15 to 997, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to $a + 14$.	
716835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1319 of SEQ ID NO:78, b is an integer of 15 to 1333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to $a + 14$.	
716947	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 546 of SEQ ID NO:79, b is an integer of 15 to 560, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to $a + 14$.	
717685	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 3189 of SEQ ID NO:80, b is an integer of 15 to 3203, where both a	T54040, N35800, W45088, AA122232, AA121109, AA126030, AA126152, AA155618, AA155656

	and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.	
719755	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1696 of SEQ ID NO:81, b is an integer of 15 to 1710, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.	
720389	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1365 of SEQ ID NO:82, b is an integer of 15 to 1379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.	
720903	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 664 of SEQ ID NO:83, b is an integer of 15 to 678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.	
721348	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2789 of SEQ ID NO:84, b is an integer of 15 to 2803, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.	
721562	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	

	formula of a-b, where a is any integer between 1 to 1264 of SEQ ID NO:85, b is an integer of 15 to 1278, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.	
722775	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2571 of SEQ ID NO:86, b is an integer of 15 to 2585, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.	
724463	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 371 of SEQ ID NO:87, b is an integer of 15 to 385, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.	
727501	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2486 of SEQ ID NO:88, b is an integer of 15 to 2500, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.	
728418	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1395 of SEQ ID NO:89, b is an integer of 15 to 1409, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.	
728920	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1322 of SEQ ID NO:90, b is an integer of 15 to 1336, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.	
732958	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 773 of SEQ ID NO:91, b is an integer of 15 to 787, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.	
733134	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1643 of SEQ ID NO:92, b is an integer of 15 to 1657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.	T49547, T49558, T49559, T49560, T49561, T49649, T49650, T70062, T70129, T75532, T95137, R17573, T27052, R19790, R42912, R52618, R53272, R42912, R59922, R59923, R65930, H08841, H08925, H47546, H47547, H47774, H47784, H48119, H64949, H64950, H69959, H69960, H80517, H80569, H81281, H81337, H87618, H87619, H88959, H89042, H95657, H95712, H95729, H88959, H98860, N20108, N23582, N27446, N34733, N49675, N51841, N75517, N78965, N93975, W05310, W17334, W40344, W52084, W52929, W72818, W72819, W86046, W92307, W92294, AA009783, AA009892, AA022930, AA022980, AA024699, AA024734, AA037408, AA045887, AA045888, AA062821, AA081026, AA082088, AA082420, AA102801, AA199861, AA199931, AA220961, AA223217, AA223456, AA224153, AA224177, AA224137, AA224138, AA224341, AA232349, AA232533, AA232117, AA458900, AA459095, AA463299
734099	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 471 of SEQ ID NO:93, b is an integer of 15 to 485, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or	R22895, H87448

	equal to $a + 14$.	
734599	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 750 of SEQ ID NO:94, b is an integer of 15 to 764, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to $a + 14$.	
736019	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 693 of SEQ ID NO:95, b is an integer of 15 to 707, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to $a + 14$.	T41219, T50359, T56829, T58426, T58458, T60928, T60984, T64158, T64287, R27157, H03484, H03579, H22546, H22547, H28310, H44067, H44146, R83796, H48481, H48645, H57243, H66162, H66163, H82370, N21110, N21188, N27461, N29155, N29743, N31124, N32398, N39884, N56818, N57165, N57228, N57403, N68904, N73978, N77833, N93027, N93818, N67112, W00894, W00923, W02234, W16676, W21379, W44969, AA064843, AA070697, AA070876, AA071332, AA071265, AA076379, AA076308, AA079524, AA079572, AA081231, AA081401, AA083774, AA083775, AA130308, AA130309, AA132056, AA132160, AA143132, AA146882, AA146883, AA165057, AA164722, AA166939, AA181133, AA187371, AA187804, AA188118, AA186447, AA186448, AA187105, AA187150, AA188273
738268	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 801 of SEQ ID NO:96, b is an integer of 15 to 815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to $a + 14$.	T48287, T48288, T54477, T54511, R34064, R36907, R49496, R49496, R75625, R75724, H12225, H16384, H19466, H19543, H42166, H42988, H54780, H99297, N22733, N26471, N74933, N93468, W15461, W47542, W47590, N90997, AA010700, AA010701, AA056728, AA088699, AA126219, AA132934, AA156291, AA165516, AA165558, AA176293, AA173448, AA189056, AA233515, AA459831, AA460011
738911	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 644 of SEQ ID NO:97, b is an integer of 15 to 658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to $a + 14$.	H22593, H52836

739226	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 235 of SEQ ID NO:98, b is an integer of 15 to 249, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.	T57824, N63155, AA027845
739527	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 738 of SEQ ID NO:99, b is an integer of 15 to 752, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.	
740710	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3045 of SEQ ID NO:100, b is an integer of 15 to 3059, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.	
742980	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1668 of SEQ ID NO:101, b is an integer of 15 to 1682, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.	T71993, R12901, R40053, H14591, H14696, R83485, H50584, H50585, H89958, H89966, H89973, H89980, N26005, N34777, N36638, N36637, N44503, N67682, N76121, N79613, W03491, W05571, W31276, W49653, W49727, AA009708, AA009798, AA035612, AA042894, AA043030, AA062953, AA115370, AA133278, AA181268, AA181269, AA193206
744331	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 924 of SEQ ID NO:102, b is an integer of 15 to 938, where both a and b correspond to the positions of	R25354, R49789, R71735, R71740, H73502, H79224, H87423, H99515, H99516, N24751, N32707, N44511, N52325, N67764, N75095, N93879, W40372, W69127, W69094, W74698, W74736, AA026984, AA035176, AA149088, AA262739, AA464357, AA430724

	nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.	
744751	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1998 of SEQ ID NO:103, b is an integer of 15 to 2012, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.	
745750	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1080 of SEQ ID NO:104, b is an integer of 15 to 1094, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.	
746285	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2283 of SEQ ID NO:105, b is an integer of 15 to 2297, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.	T87719, T87928, R99975, R99976, H64714, H65205, H92423, H65205, N47296, N48612, N58085, N58926, N64294, N64508, N72401, N80294, N93405, W04791, W21447, W94582, W95317, AA024856, AA024939, AA037672, AA037673, AA070416, AA075508, AA075507, AA101263, AA148029, AA147953, AA169726, AA171461, AA173095, AA464821
746416	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 428 of SEQ ID NO:106, b is an integer of 15 to 442, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14.	
747851	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	N44767, W44754

	between 1 to 1005 of SEQ ID NO:107, b is an integer of 15 to 1019, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:107, and where b is greater than or equal to a + 14.	
750632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 697 of SEQ ID NO:108, b is an integer of 15 to 711, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to a + 14.	H48882, W23677, W35110, AA133857
751315	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 729 of SEQ ID NO:109, b is an integer of 15 to 743, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:109, and where b is greater than or equal to a + 14.	
754009	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 781 of SEQ ID NO:110, b is an integer of 15 to 795, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:110, and where b is greater than or equal to a + 14.	
754634	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1318 of SEQ ID NO:111, b is an integer of 15 to 1332, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:111, and where b is greater than or equal to a + 14.	N21429
756637	Preferably excluded from the present invention are one or more	N44651, W76461

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 729 of SEQ ID NO:112, b is an integer of 15 to 743, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:112, and where b is greater than or equal to a + 14.	
756833	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1676 of SEQ ID NO:113, b is an integer of 15 to 1690, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:113, and where b is greater than or equal to a + 14.	
756878	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 606 of SEQ ID NO:114, b is an integer of 15 to 620, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:114, and where b is greater than or equal to a + 14.	R12122
757332	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 528 of SEQ ID NO:115, b is an integer of 15 to 542, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:115, and where b is greater than or equal to a + 14.	
760835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 511 of SEQ ID NO:116, b is an integer of 15 to 525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:116, and where b is greater than or	

	equal to $a + 14$.	
761760	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 714 of SEQ ID NO:117, b is an integer of 15 to 728, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:117, and where b is greater than or equal to $a + 14$.	
762520	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 934 of SEQ ID NO:118, b is an integer of 15 to 948, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:118, and where b is greater than or equal to $a + 14$.	T86617, T86618, R47814, R49961, R71921, R71968, H28225, H28275, R94939, R95025, R97173, R97174, R99726, R99904, H52435, H52436, H58879, H58880, H66345, H66395, H80709, H80710, W87663, W87664, AA046620, AA046867, AA055456, AA102380, AA121314, AA150579, AA197300
764461	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 197 of SEQ ID NO:119, b is an integer of 15 to 211, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:119, and where b is greater than or equal to $a + 14$.	
764517	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1294 of SEQ ID NO:120, b is an integer of 15 to 1308, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:120, and where b is greater than or equal to $a + 14$.	
765132	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2502 of SEQ ID NO:121, b is an integer of 15 to 2516, where both	

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:121, and where b is greater than or equal to a + 14.	
765667	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1125 of SEQ ID NO:122, b is an integer of 15 to 1139, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:122, and where b is greater than or equal to a + 14.	T81691, N27595
767113	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2100 of SEQ ID NO:123, b is an integer of 15 to 2114, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:123, and where b is greater than or equal to a + 14.	
767204	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 569 of SEQ ID NO:124, b is an integer of 15 to 583, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:124, and where b is greater than or equal to a + 14.	
767400	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1973 of SEQ ID NO:125, b is an integer of 15 to 1987, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:125, and where b is greater than or equal to a + 14.	
767962	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T59753, R21255, R21256, R23274, R23364, R71913, R71956, H12633, H12686, H99087, N26954, N33518, N43798, N62998, N66835, N71124, N71156, N74144, N79907, W01554,

	formula of a-b, where a is any integer between 1 to 1437 of SEQ ID NO:126, b is an integer of 15 to 1451, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:126, and where b is greater than or equal to a + 14.	W05537, W19994, W44368, W46357, W46193, W47163, W47284, W52537, W55854, W80804, W80878, W92021, W92022, N90420. AA002178, AA022578, AA022579, AA029899, AA029987, AA034181, AA036856, AA036913, AA043237, AA043566, AA071518, AA082340, AA122159, AA120962, AA146944, AA147449, AA148081, AA151266, AA151267, AA156459
768040	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1220 of SEQ ID NO:127, b is an integer of 15 to 1234, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:127, and where b is greater than or equal to a + 14.	
769956	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 849 of SEQ ID NO:128, b is an integer of 15 to 863, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:128, and where b is greater than or equal to a + 14.	R68817, R68925, R75906, H14626, H82146, H93109, H93237, N32098, N35721, N45410, N75570, W03043, W04850, AA029607, AA262861, AA463956, AA464092
770133	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1224 of SEQ ID NO:129, b is an integer of 15 to 1238, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:129, and where b is greater than or equal to a + 14.	
770289	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 365 of SEQ ID NO:130, b is an integer of 15 to 379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:130, and where b is greater than or equal to a + 14.	

771964	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1772 of SEQ ID NO:131, b is an integer of 15 to 1786, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:131, and where b is greater than or equal to a + 14.</p>	<p>T53984, T55243, T51230, T77632, T91326, T80819, T81219, T84909, T95454, T97320, T99226, T99269, R16575, R16634, R19765, R22987, R23096, R33095, R33188, R37437, R39255, R45185, R45185, R62594, R62642, H03891, H03892, H08679, H08680, H20556, H20650, H46154, H46155, R88298, R90733, R90759, R92224, R92332, R97325, H57663, H58503, H61709, H61913, H62747, H66685, H68924, H68954, H80053, H83342, H95786, H96135, N20464, N20472, N24026, N25491, N35235, N35419, N38769, N44900, N48399, N53146, N55089, N55095, N57767, N58580, N59732, N63942, N70290, N71759, N74938, N77300, N98411, W23555, W52690, W52160, W56557, W56635, W56598, W56594, W73408, W74230, W79843, W93916, AA031492, AA070868, AA071019, AA088788, AA100685, AA112926, AA176829, AA176851, AA193034, AA194065, AA194180, AA194579, AA194703, AA195416, AA195532, AA233792, AA233783, AA233900, AA233920, AA234128, AA234169, AA252704, AA252831, AA416743, AA418391, AA418440</p>
772582	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 960 of SEQ ID NO:132, b is an integer of 15 to 974, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:132, and where b is greater than or equal to a + 14.</p>	
773387	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 620 of SEQ ID NO:133, b is an integer of 15 to 634, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:133, and where b is greater than or equal to a + 14.</p>	
773827	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1841 of SEQ ID NO:134,</p>	

	b is an integer of 15 to 1855, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:134, and where b is greater than or equal to a + 14.	
774108	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 903 of SEQ ID NO:135, b is an integer of 15 to 917, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:135, and where b is greater than or equal to a + 14.	T96288, R31388, R32886, R63543, R63597, R75811, R75812, H20285, H20509, H20599, H21238, H24872, H29854, H29945, H41103, H41208, H44188, H44189, R85628, R91367, H83459, H83571, H97165, H97164, N25639, N29652, N29777, N32407, N32413, N32580, N32835, N41918, N42281, N56607, N57152, N57196, N69818, N70613, N93340, N93928, N94454, W24358, W25163, W30800, W37904, W37964, W40428, W68631, W68632, W70339, W80994, W81096, W81716, W81253, W81543, W81544, W94206, AA004372, AA011346, AA016002, AA028888, AA029626, AA029627, AA044028, AA044350, AA062804, AA081035, AA131270, AA131354, AA131371
774636	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1257 of SEQ ID NO:136, b is an integer of 15 to 1271, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:136, and where b is greater than or equal to a + 14.	T54747, T69827, R14146, R50592, R55502, R73615, R73937, H41540, R84981, R85103, R87495, R88553, R88554, R88556, R88818, R88839, R89675, R91235, H51003, H51004, H51581, H79057, N70799, W02680, AA232327, AA232417, AA464467
775339	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2003 of SEQ ID NO:137, b is an integer of 15 to 2017, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:137, and where b is greater than or equal to a + 14.	
775582	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 923 of SEQ ID NO:138, b is an integer of 15 to 937, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:138, and where b is greater than or	T62486, T62631, H14642, R85991, H73603, N54912, N68727, N80228, N91617, W38518, W67302, W67418, AA171395, AA214500, AA215291, AA464035

	equal to $a + 14$.	
775779	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 2745 of SEQ ID NO:139, b is an integer of 15 to 2759, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:139, and where b is greater than or equal to $a + 14$.	
777809	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1227 of SEQ ID NO:140, b is an integer of 15 to 1241, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:140, and where b is greater than or equal to $a + 14$.	
778927	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 3391 of SEQ ID NO:141, b is an integer of 15 to 3405, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:141, and where b is greater than or equal to $a + 14$.	T50777, T50939, R11800, R19713, R31403, R32898, R44269, R44269, R55431, R60041, R60103, R69554, R74340, R74434, H20427, H26615, H26660, H42495, H43482, R85644, H51488, H68618, N58157, N58231, N77611, W39692, W45048, W56828, W57633, AA052900, AA057808, AA074705, AA122120, AA121079, AA121231, AA259051, AA464470
779262	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 2254 of SEQ ID NO:142, b is an integer of 15 to 2268, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:142, and where b is greater than or equal to $a + 14$.	R11844, R71241, R71292, H00159, H88551, H90726, H98059, N28770, N58442, N78033, W32671, AA035075, AA112651, AA112652, AA130035, AA215309, AA251209
779392	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1743 of SEQ ID NO:143, b is an integer of 15 to 1757, where both	R25284, R36255, R36256, R42970, R46635, R42970, R46635, H28773, N52867, N70541, N77890, W05403, W05783, AA085067, AA085066, AA204650, AA210753, AA211713, AA251462, AA252456, AA460350, AA460780

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:143, and where b is greater than or equal to a + 14.	
780149	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1048 of SEQ ID NO:144, b is an integer of 15 to 1062, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:144, and where b is greater than or equal to a + 14.	
780583	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1016 of SEQ ID NO:145, b is an integer of 15 to 1030, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:145, and where b is greater than or equal to a + 14.	
780960	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 800 of SEQ ID NO:146, b is an integer of 15 to 814, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:146, and where b is greater than or equal to a + 14.	
781469	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2664 of SEQ ID NO:147, b is an integer of 15 to 2678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:147, and where b is greater than or equal to a + 14.	T95791, H18820, H19074, H22604, H40723, H45802, H46056, H47074, H47156, H86819, H86886, H88675, H88724, H88972, H89058, H88972, N28987, N36053, N39668, N47281, W19145, W68543, W68544, N91577, AA044679, AA044896, AA430011
781556	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T94861, T94906, R21516, R26869, R27098, R36258, R37965, R37966, R78172, H03413, H04116, H14531, H45546, R96826, R98130, N51409, N52365, N64272, N74939, N75136,

	formula of a-b, where a is any integer between 1 to 1014 of SEQ ID NO:148, b is an integer of 15 to 1028, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:148, and where b is greater than or equal to a + 14.	W23556, W35208, AA187823, AA191525, AA429367
781771	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1411 of SEQ ID NO:149, b is an integer of 15 to 1425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:149, and where b is greater than or equal to a + 14.	T95420, T99529, R50341, R52125, R72608, R72630, R72677, R72701, H26733, H26734, H30106, H59788, H82441, N75150, W42750, W42840
782033	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 766 of SEQ ID NO:150, b is an integer of 15 to 780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:150, and where b is greater than or equal to a + 14.	H53100, H53207, H97410, H98035, N30753, N68541, W42491, W42641, W57808, AA046603, AA046753, AA136886, AA136997, AA143419, AA143420
782105	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:151, b is an integer of 15 to 1066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:151, and where b is greater than or equal to a + 14.	R97486, H72940, W90139
782122	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1635 of SEQ ID NO:152, b is an integer of 15 to 1649, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:152, and where b is greater than or equal to a + 14.	T54379, T60348, T61029, T54271, T57801, R10793, T78907, T78959, R49078, R55635, R67844, R67845, R69587, R72600, R72666, H04742, H04830, H16978, H24654, H26129, H26308, H26395, H26467, H28100, H28205, H28252, H28895, H28896, H30485, H39554, H42595, H42603, H42662, H43740, H44345, H44346, H44546, H44547, H44960, H45012, H45860, R88120, R88214, H51204, H58080, H58081, H64553, H64654, H70033, H70034, H86451, H70034, H99833, N24525, N29867, N30752, N35500, N39259, N42463, N44804,

		N52550, N53985, N57289, N58726, N63349, N67624, N67663, N68157, N70299, N80615, N93230, N94595, N98489, W19633, W23803, W25087, W31034, W37981, W37982, W42579, W44389, W49677, W57614, W57871, W58142, W67781, W67840, W68147, W68474, W68699, W68791, W69717, W80749, W80837, N89879, AA025233, AA025568, AA025686, AA026020, AA033846, AA039625, AA039693, AA046842, AA047013, AA057608, AA057676, AA064637, AA064680, AA074448, AA083591, AA098837, AA102142, AA113374, AA113402, AA115525, AA114948, AA128972, AA128973, AA133142, AA146949, AA148086, AA149283, AA149377, AA160012, AA160688, AA172144, AA180932, AA182561
783135	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 646 of SEQ ID NO:153, b is an integer of 15 to 660, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:153, and where b is greater than or equal to a + 14.	
783245	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 591 of SEQ ID NO:154, b is an integer of 15 to 605, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:154, and where b is greater than or equal to a + 14.	
783247	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 681 of SEQ ID NO:155, b is an integer of 15 to 695, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:155, and where b is greater than or equal to a + 14.	AA155638
783413	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	H58751, H93683, H93684, N93167, W19186, W19958, W38771, N91367

	sequence described by the general formula of a-b, where a is any integer between 1 to 766 of SEQ ID NO:156, b is an integer of 15 to 780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:156, and where b is greater than or equal to a + 14.	
784407	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1113 of SEQ ID NO:157, b is an integer of 15 to 1127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:157, and where b is greater than or equal to a + 14.	
784548	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1268 of SEQ ID NO:158, b is an integer of 15 to 1282, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:158, and where b is greater than or equal to a + 14.	
785075	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1491 of SEQ ID NO:159, b is an integer of 15 to 1505, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:159, and where b is greater than or equal to a + 14.	
785677	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 722 of SEQ ID NO:160, b is an integer of 15 to 736, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:160, and where b is greater than or equal to a + 14.	

786238	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 981 of SEQ ID NO:161, b is an integer of 15 to 995, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:161, and where b is greater than or equal to a + 14.	
786389	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1111 of SEQ ID NO:162, b is an integer of 15 to 1125, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:162, and where b is greater than or equal to a + 14.	
786929	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 409 of SEQ ID NO:163, b is an integer of 15 to 423, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:163, and where b is greater than or equal to a + 14.	
786932	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1628 of SEQ ID NO:164, b is an integer of 15 to 1642, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:164, and where b is greater than or equal to a + 14.	
787078	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1101 of SEQ ID NO:165, b is an integer of 15 to 1115, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:165, and where b is greater than or equal to a + 14.	
787139	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:166, b is an integer of 15 to 1066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:166, and where b is greater than or equal to a + 14.	
787283	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:167, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:167, and where b is greater than or equal to a + 14.	R22724
788761	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1012 of SEQ ID NO:168, b is an integer of 15 to 1026, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:168, and where b is greater than or equal to a + 14.	
788988	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 760 of SEQ ID NO:169, b is an integer of 15 to 774, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:169, and where b is greater than or equal to a + 14.	
789092	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	AA234588

	between 1 to 388 of SEQ ID NO:170, b is an integer of 15 to 402, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:170, and where b is greater than or equal to a + 14.	
789298	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 782 of SEQ ID NO:171, b is an integer of 15 to 796, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:171, and where b is greater than or equal to a + 14.	
789299	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:172, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:172, and where b is greater than or equal to a + 14.	
789718	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 642 of SEQ ID NO:173, b is an integer of 15 to 656, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:173, and where b is greater than or equal to a + 14.	
789957	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1877 of SEQ ID NO:174, b is an integer of 15 to 1891, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:174, and where b is greater than or equal to a + 14.	T51260, T61941, T62167, T77034, T90753, R38108, N32708, N92379, W24621, W42543, W42478, AA128007, AA128031, AA134234, AA424998
789977	Preferably excluded from the present invention are one or more	T56442, T78292, R37940, R56008, R56009, R56573, R56574, H11080, N34431, N48665,

	<p>polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2147 of SEQ ID NO:175, b is an integer of 15 to 2161, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:175, and where b is greater than or equal to a + 14.</p>	AA010749, AA011177, AA070806, AA070882, AA146859, AA147636, AA147691, AA164223, AA164224, AA210729, AA210859, AA243063, AA243070, AA464493, AA464494
790285	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2397 of SEQ ID NO:176, b is an integer of 15 to 2411, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:176, and where b is greater than or equal to a + 14.</p>	T66279, T66328, T84164, T85098, R24232, R24233, H03657, H03658, H98526, H98556, H99618, N22728, N29400, N32172, N33953, N41460, N69471, N70552, N73722, W03893, W44579, W72407, W76486, W78102, W79410, N90963, AA044816, AA044841, AA086039, AA086121, AA088877, AA102298, AA130887, AA131529, AA131603, AA181784, AA182515, AA190450, AA191392, AA223757
790509	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1324 of SEQ ID NO:177, b is an integer of 15 to 1338, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:177, and where b is greater than or equal to a + 14.</p>	T68040, H17760, AA101036, AA129837
790775	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1600 of SEQ ID NO:178, b is an integer of 15 to 1614, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:178, and where b is greater than or equal to a + 14.</p>	N25320, N31432, W81044, W81097
790888	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4278 of SEQ ID NO:179, b is an integer of 15 to 4292, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:179, and where b is greater than or</p>	R14550, R15204, T26493, R21597, R22908, R23010, R41211, R41649, R43371, R41211, R41649, R43371, R58989, R59048, H05739, H05845, H17266, H17265, H23579, H44104, H46505, H47043, H58955, H59002, H73676, H73730, H80078, H82275, H82289, H82399, H82381, H97810, H98133, H98737, N23117, N24310, N25196, N25265, N27792, N28735, N29893, N33395, N33904, N36066, N36839, N42542, N46060, N51230, N59535, N67737,

	equal to $a + 14$.	N73641, N78481, N78694, W03555, W15202, W52445, W52723, W95124, AA047257, AA057142, AA204699, AA251464, AA430598
791506	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 229 of SEQ ID NO:180, b is an integer of 15 to 243, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:180, and where b is greater than or equal to $a + 14$.	
791649	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 799 of SEQ ID NO:181, b is an integer of 15 to 813, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:181, and where b is greater than or equal to $a + 14$.	
791802	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 808 of SEQ ID NO:182, b is an integer of 15 to 822, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:182, and where b is greater than or equal to $a + 14$.	
792002	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1081 of SEQ ID NO:183, b is an integer of 15 to 1095, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:183, and where b is greater than or equal to $a + 14$.	T49735, T49736, T95310, T95391, T99384, T99612, R63493, R63494, H27739, R91698, R92136, H52608, H57619, H58464, H61415, H62139, H69019, H87167, H87669, N21358, N70307, N79596, W19063, W58498, W58651, W79687, W81289, AA099849, AA099972, AA232767
792291	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer	T55436, R21797, R22403, R22452, R22916, R23020, R76901, R77068, H22573, H25752, H25866, R83900, H50717, H50821, H64026, H64791, H95702, N64545, N69769, N74704, N80341, W05092, W79489, W79634,

	between 1 to 3661 of SEQ ID NO:184, b is an integer of 15 to 3675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:184, and where b is greater than or equal to a + 14.	AA005055, AA005007, AA025043, AA036711, AA037127, AA043916, AA055100, AA063627, AA069142, AA069230, AA069323, AA069376, AA112277, AA112531, AA115279, AA151238, AA151239, AA151582, AA149398, AA149961, AA150069, AA158029, AA158321, AA158692, AA158693, AA161232, AA236787, AA236834, AA256776, AA261961
792371	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1026 of SEQ ID NO:185, b is an integer of 15 to 1040, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:185, and where b is greater than or equal to a + 14.	
792660	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 803 of SEQ ID NO:186, b is an integer of 15 to 817, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:186, and where b is greater than or equal to a + 14.	T59054, T86590, T83271, R48677, R53483, R53482, R62329, R62330, R66651, R67372, R69095, R69210, R71144, R82632, R82676, H15764, H15765, H19518, H19605, H27898, H42872, H42936, H49329, H49330, H50062, H50061, H87268, H87324, H96667, N22675, N92574, W37223, W37563, W38866, W61119, W65380, AA035095, AA035635, AA037254, AA054951, AA062973, AA082301, AA132472
792782	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1066 of SEQ ID NO:187, b is an integer of 15 to 1080, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:187, and where b is greater than or equal to a + 14.	
792890	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1272 of SEQ ID NO:188, b is an integer of 15 to 1286, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:188, and where b is greater than or equal to a + 14.	AA251351

792931	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1724 of SEQ ID NO:189, b is an integer of 15 to 1738, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:189, and where b is greater than or equal to a + 14.	
792943	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1909 of SEQ ID NO:190, b is an integer of 15 to 1923, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:190, and where b is greater than or equal to a + 14.	
793104	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 236 of SEQ ID NO:191, b is an integer of 15 to 250, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:191, and where b is greater than or equal to a + 14.	
793445	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1888 of SEQ ID NO:192, b is an integer of 15 to 1902, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:192, and where b is greater than or equal to a + 14.	AA034998, AA044249, AA088830, AA429418
793446	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 546 of SEQ ID NO:193, b is an integer of 15 to 560, where both a and b correspond to the positions of	T57765, T60664, H01264, H45774, H54790, H54842, H64484, H64485, N98810, W58332, W58653, W74582, W79320, W79420, W79565, W92452, AA027210, AA027209, AA029725, AA029663, AA088693, AA121506, AA127731, AA428362

	nucleotide residues shown in SEQ ID NO:193, and where b is greater than or equal to a + 14.	
793639	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 576 of SEQ ID NO:194, b is an integer of 15 to 590, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:194, and where b is greater than or equal to a + 14.	N69881, N93023, N98853, W21375, W73944, W77988, AA169530, AA169837, AA176453, AA176931
794213	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 677 of SEQ ID NO:195, b is an integer of 15 to 691, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:195, and where b is greater than or equal to a + 14.	N53897, N55318
795858	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1758 of SEQ ID NO:196, b is an integer of 15 to 1772, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:196, and where b is greater than or equal to a + 14.	
795955	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 661 of SEQ ID NO:197, b is an integer of 15 to 675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:197, and where b is greater than or equal to a + 14.	
796359	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 543 of SEQ ID NO:198, b is an integer of 15 to 557, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:198, and where b is greater than or equal to a + 14.	
796555	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2597 of SEQ ID NO:199, b is an integer of 15 to 2611, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:199, and where b is greater than or equal to a + 14.	T69136, T69194, T95612, T95713, R53091, R73126, N41876, N49174, W05348, W04725, W31397, W31827, W92674, AA039513
796675	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2302 of SEQ ID NO:200, b is an integer of 15 to 2316, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:200, and where b is greater than or equal to a + 14.	
796743	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1133 of SEQ ID NO:201, b is an integer of 15 to 1147, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:201, and where b is greater than or equal to a + 14.	
796792	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 674 of SEQ ID NO:202, b is an integer of 15 to 688, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:202, and where b is greater than or equal to a + 14.	
799668	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 290 of SEQ ID NO:203, b is an integer of 15 to 304, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:203, and where b is greater than or equal to a + 14.	
799669	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 403 of SEQ ID NO:204, b is an integer of 15 to 417, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:204, and where b is greater than or equal to a + 14.	
799673	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 537 of SEQ ID NO:205, b is an integer of 15 to 551, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:205, and where b is greater than or equal to a + 14.	
799674	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1087 of SEQ ID NO:206, b is an integer of 15 to 1101, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:206, and where b is greater than or equal to a + 14.	
799678	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 501 of SEQ ID NO:207, b is an integer of 15 to 515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:207, and where b is greater than or	

	equal to $a + 14$.	
799728	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 255 of SEQ ID NO:208, b is an integer of 15 to 269, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:208, and where b is greater than or equal to $a + 14$.	
799748	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 720 of SEQ ID NO:209, b is an integer of 15 to 734, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:209, and where b is greater than or equal to $a + 14$.	H19497, H19579, H50117, H50164, H52826, H52827, H61184, H62087, H96290, H96291, N20586, N21261, N28978, N30137, N30490, N35750, W31933, W37535, N90542, AA418545, AA418511
799760	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 644 of SEQ ID NO:210, b is an integer of 15 to 658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:210, and where b is greater than or equal to $a + 14$.	
799805	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 190 of SEQ ID NO:211, b is an integer of 15 to 204, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:211, and where b is greater than or equal to $a + 14$.	
800296	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1257 of SEQ ID NO:212, b is an integer of 15 to 1271, where both	

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:212, and where b is greater than or equal to a + 14.	
800327	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1011 of SEQ ID NO:213, b is an integer of 15 to 1025, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:213, and where b is greater than or equal to a + 14.	
800816	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 337 of SEQ ID NO:214, b is an integer of 15 to 351, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:214, and where b is greater than or equal to a + 14.	
800835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1073 of SEQ ID NO:215, b is an integer of 15 to 1087, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:215, and where b is greater than or equal to a + 14.	
805429	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1963 of SEQ ID NO:216, b is an integer of 15 to 1977, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:216, and where b is greater than or equal to a + 14.	
805458	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T82438, T82439, R19121, R20391, R28602, R36743, R43508, R46035, R43508, R46035, R79588, H24625, N28372, N28785, N29421, N35476, N57353, N72836, N79096, W03034,

	formula of a-b, where a is any integer between 1 to 2801 of SEQ ID NO:217, b is an integer of 15 to 2815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:217, and where b is greater than or equal to a + 14.	AA016073, AA019733, AA021030, AA062895, AA081968, AA115692, AA133511, AA151852, AA149707, AA194903, AA194902
805478	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1631 of SEQ ID NO:218, b is an integer of 15 to 1645, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:218, and where b is greater than or equal to a + 14.	
805805	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:219, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:219, and where b is greater than or equal to a + 14.	
806486	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 818 of SEQ ID NO:220, b is an integer of 15 to 832, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:220, and where b is greater than or equal to a + 14.	
806498	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1878 of SEQ ID NO:221, b is an integer of 15 to 1892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:221, and where b is greater than or equal to a + 14.	
806819	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 854 of SEQ ID NO:222, b is an integer of 15 to 868, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:222, and where b is greater than or equal to a + 14.	
810870	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1502 of SEQ ID NO:223, b is an integer of 15 to 1516, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:223, and where b is greater than or equal to a + 14.	R50267, R50730, H27672, H27673, H30138, H99256, N74342, N80868, W05054, W07601
811730	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1292 of SEQ ID NO:224, b is an integer of 15 to 1306, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:224, and where b is greater than or equal to a + 14.	
813025	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 570 of SEQ ID NO:225, b is an integer of 15 to 584, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:225, and where b is greater than or equal to a + 14.	
813233	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 509 of SEQ ID NO:226, b is an integer of 15 to 523, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:226, and where b is greater than or equal to a + 14.	
813262	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2363 of SEQ ID NO:227, b is an integer of 15 to 2377, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:227, and where b is greater than or equal to a + 14.	
815637	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 449 of SEQ ID NO:228, b is an integer of 15 to 463, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:228, and where b is greater than or equal to a + 14.	
815853	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1218 of SEQ ID NO:229, b is an integer of 15 to 1232, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:229, and where b is greater than or equal to a + 14.	R53293, R59708, R59818, R88929, R89609, H78819, N52182, AA125808, AA128281
815999	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1049 of SEQ ID NO:230, b is an integer of 15 to 1063, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:230, and where b is greater than or equal to a + 14.	
823427	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1049 of SEQ ID NO:231.	T53986, T60846, T72425, R18752, H22479, H50211, N40817, N93431, W21474, W21308, W32281, W44860, W95821, N90881, AA132037, AA131965, AA151157, AA155868, AA156600, AA156837, AA157061, AA157045, AA160623, AA169460, AA176447, AA178894,

	b is an integer of 15 to 1063, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:231, and where b is greater than or equal to a + 14.	AA179764, AA180438, AA181145, AA181144, AA196382, AA196478
823704	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1460 of SEQ ID NO:232, b is an integer of 15 to 1474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:232, and where b is greater than or equal to a + 14.	
824798	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1768 of SEQ ID NO:233, b is an integer of 15 to 1782, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:233, and where b is greater than or equal to a + 14.	
825018	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2194 of SEQ ID NO:234, b is an integer of 15 to 2208, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:234, and where b is greater than or equal to a + 14.	
825076	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2566 of SEQ ID NO:235, b is an integer of 15 to 2580, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:235, and where b is greater than or equal to a + 14.	
825787	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	

	sequence described by the general formula of a-b, where a is any integer between 1 to 2994 of SEQ ID NO:236, b is an integer of 15 to 3008, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:236, and where b is greater than or equal to a + 14.	
826116	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 863 of SEQ ID NO:237, b is an integer of 15 to 877, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:237, and where b is greater than or equal to a + 14.	
826147	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3025 of SEQ ID NO:238, b is an integer of 15 to 3039, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:238, and where b is greater than or equal to a + 14.	
827020	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1978 of SEQ ID NO:239, b is an integer of 15 to 1992, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:239, and where b is greater than or equal to a + 14.	
827586	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 483 of SEQ ID NO:240, b is an integer of 15 to 497, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:240, and where b is greater than or equal to a + 14.	

827732	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 302 of SEQ ID NO:241, b is an integer of 15 to 316, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:241, and where b is greater than or equal to a + 14.	
827735	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 815 of SEQ ID NO:242, b is an integer of 15 to 829, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:242, and where b is greater than or equal to a + 14.	
827740	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 824 of SEQ ID NO:243, b is an integer of 15 to 838, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:243, and where b is greater than or equal to a + 14.	R21513, R22316, R42033, R43706, R42033, R43706, R63113, R70954, R71006, N48618, N53377, AA912400
827808	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2839 of SEQ ID NO:244, b is an integer of 15 to 2853, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:244, and where b is greater than or equal to a + 14.	
828251	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1183 of SEQ ID NO:245, b is an integer of 15 to 1197, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:245, and where b is greater than or equal to a + 14.	
828357	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 834 of SEQ ID NO:246, b is an integer of 15 to 848, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:246, and where b is greater than or equal to a + 14.	
828449	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1322 of SEQ ID NO:247, b is an integer of 15 to 1336, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:247, and where b is greater than or equal to a + 14.	
828612	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1062 of SEQ ID NO:248, b is an integer of 15 to 1076, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:248, and where b is greater than or equal to a + 14.	R28513, R28661, R31336, R41867, R41867, R60004, H19945, H19946, H22061, H46271, H46342, H82619, H82618, N20678, W96169, AA010842, AA278855, AA582295, AA583721, AA639735, AA579409, AA568321, AA833752, AA907437, AI054389, W22584
828647	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2411 of SEQ ID NO:249, b is an integer of 15 to 2425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:249, and where b is greater than or equal to a + 14.	
828698	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 1394 of SEQ ID NO:250, b is an integer of 15 to 1408, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:250, and where b is greater than or equal to a + 14.	
828962	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 480 of SEQ ID NO:251, b is an integer of 15 to 494, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:251, and where b is greater than or equal to a + 14.	
828982	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2477 of SEQ ID NO:252, b is an integer of 15 to 2491, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:252, and where b is greater than or equal to a + 14.	T64550, T65973, T94849, T94894, R07359, R07409, R34782, R35670, R35781, R56137, R56532, R64039, R66397, R67131, H01215, H02256, H02354, H03227, H04019, R94572, R94573, H51242, H60286, H65939, H72416, H72857, N22537, N24628, N24936, N33813, N35712, N35830, N35916, N43982, N51363, N64462, N70838, N75470, N75760, W01444, W05279, W57605, W58752, W72612, W72970, W73260, W73535, W76678, W76207, W94918, W91971, W92319, W92355, AA024690, AA024643, AA028083, AA028084, AA028169, AA035743, AA045830, AA045917, AA081723, AA086310, AA085740, AA102651, AA101305, AA126788, AA126837, AA126865, AA127295, AA129688, AA129664, AA133503, AA133504, AA132801, AA134537, AA134547, AA186712, AA188264, AA215597, AA463977, AA464112, AA417286, AA417312, AA259228, AA279952, AA287814, AA468227, AA468302, AA526480, AA553703, AA587072, AA635683, AA639361, AA573471, AA579754, AA579812, AA580600, AA730425, AA741436, AA804629, AA829189, AA830255, AA865594, AA885821, AA918979, AA962033, AA985542, AA985571, AA987607, AA995783, A1075334, D79160, N84712, N88655, C03235, AA094028
829282	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1111 of SEQ ID NO:253, b is an integer of 15 to 1125, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:253, and where b is greater than or equal to a + 14.	
829368	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1395 of SEQ ID NO:254, b is an integer of 15 to 1409, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:254, and where b is greater than or equal to a + 14.	R61547, R76124, H01565, H02950, H04248, H29996, H99672, W19970
829751	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 476 of SEQ ID NO:255, b is an integer of 15 to 490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:255, and where b is greater than or equal to a + 14.	
829773	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1219 of SEQ ID NO:256, b is an integer of 15 to 1233, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:256, and where b is greater than or equal to a + 14.	T96982, T97094, H53488, H53861, H64894, H65486, N62304, N67480, N78709, W03409, W07598, W73770, AA025496, AA025812, AA133948
829934	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2390 of SEQ ID NO:257, b is an integer of 15 to 2404, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:257, and where b is greater than or equal to a + 14.	
829942	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	T64541, T65964, R01423, R01424, R05277, R19450, R44699, R51779, R51780, R44699, H11322, H11349, H13859, H13911, H21393, H21437, H21890, H22117, H45982, H46047, H47137, R98886, H54491, H54854, H98744,

	between 1 to 2078 of SEQ ID NO:258, b is an integer of 15 to 2092, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:258, and where b is greater than or equal to a + 14.	N23465, N37080, N46155, N46396, N58995, N62715, N93640, W60228, W60227, W74349, W76544, W87768, W87883, W90517, W90518, AA010775, AA011055, AA029083, AA029084, AA036822, AA057660, AA075916, AA082814, AA101057, AA130702, AA132788, AA133063, AA147813, AA148063, AA151487, AA151511, AA173298, AA173348, AA181036, AA187993, AA187994, AA192370, AA192357, AA243010, AA243264, AA250948
829951	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 373 of SEQ ID NO:259, b is an integer of 15 to 387, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:259, and where b is greater than or equal to a + 14.	
830173	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3698 of SEQ ID NO:260, b is an integer of 15 to 3712, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:260, and where b is greater than or equal to a + 14.	T52493, T52572, T56913, T61268, T61320, T70063, T70130, T72005, T87844, T94182, T70248, R24534, R24639, R31200, R64161, R64274, R70751, R70750, H16189, H89274, H99749, N25430, N25537, N32578, N32816, N34120, N34134, N34491, N35081, N42260, N43821, N62152, N62798, N64065, N64169, N67362, N69808, N74678, N93912, N49165, W04704, W05040, W16565, W19920, W31806, W31907, W37354, W37355, W40493, W45266, W45455, W52925, W58628, W92222, W92345, N91265, AA027083, AA027124, AA028969, AA029137, AA029257, AA083657, AA084297, AA121151, AA121131, AA126957, AA127166, AA128353, AA128495, AA128834, AA132690, AA132783, AA136553, AA152414, AA150706, AA150808, AA156272, AA164766, AA164767, AA171427, AA171794, AA173592, AA173949, AA190421, AA190580, AA191383, AA224415, AA232135
830200	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 883 of SEQ ID NO:261, b is an integer of 15 to 897, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:261, and where b is greater than or equal to a + 14.	AA524284, AA662477, AA887924

830365	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1891 of SEQ ID NO:262, b is an integer of 15 to 1905, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:262, and where b is greater than or equal to a + 14.	R42905, R59718, R62419, R72182, R72228, H22520, H22519, H25889, H45643, H46451, H46992, H84483, N50834, N92573, AA022699, AA022791, AA037734, AA037735, AA040585, AA040557, AA047816, AA159187, AA159282, AA223337, AA505391, AA515591, AA524466, AA613383, AA627298, AA578816, AA769153, AA826456, AA830896, AA831083, AA837917, AA977053, A1083822, A1090301, A1084104
830456	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1410 of SEQ ID NO:263, b is an integer of 15 to 1424, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:263, and where b is greater than or equal to a + 14.	T39800, T39875, T40331, T80148, R01135, R05754, R12866, R15287, R21703, R39361, H00652, H00741, H05366, H17706, H23423, R97800, R97849, N25478, N41797, N48511, N98906, W19893, W23945, W35174, W60540, W78229, W79282, W84685, AA022952, AA026821, AA026953, AA074956, AA075111, AA114974, AA114988, AA192860, AA193064
830549	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1273 of SEQ ID NO:264, b is an integer of 15 to 1287, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:264, and where b is greater than or equal to a + 14.	R60171, H26796, H96303, N91699, W25137, AA069218, AA088565, AA161178
830602	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 977 of SEQ ID NO:265, b is an integer of 15 to 991, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:265, and where b is greater than or equal to a + 14.	
830610	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2306 of SEQ ID NO:266, b is an integer of 15 to 2320, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:266, and where b is greater than or equal to a + 14.	
830644	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 409 of SEQ ID NO:267, b is an integer of 15 to 423, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:267, and where b is greater than or equal to a + 14.	
830707	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1832 of SEQ ID NO:268, b is an integer of 15 to 1846, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:268, and where b is greater than or equal to a + 14.	
830709	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 587 of SEQ ID NO:269, b is an integer of 15 to 601, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:269, and where b is greater than or equal to a + 14.	
830733	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 866 of SEQ ID NO:270, b is an integer of 15 to 880, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:270, and where b is greater than or equal to a + 14.	T26638, R49962, H96664, N71762, N90691, AA040156, AA128271, AA418045, AA418216, AA535799, AA583405, AA768811
830768	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 2470 of SEQ ID NO:271, b is an integer of 15 to 2484, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:271, and where b is greater than or equal to a + 14.	
830855	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 737 of SEQ ID NO:272, b is an integer of 15 to 751, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:272, and where b is greater than or equal to a + 14.	H17127, AA100311, AA112910, AA282249, AA578649, AA748590
830949	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3295 of SEQ ID NO:273, b is an integer of 15 to 3309, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:273, and where b is greater than or equal to a + 14.	
830965	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 829 of SEQ ID NO:274, b is an integer of 15 to 843, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:274, and where b is greater than or equal to a + 14.	
830973	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2014 of SEQ ID NO:275, b is an integer of 15 to 2028, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:275, and where b is greater than or equal to a + 14.	
830979	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1441 of SEQ ID NO:276, b is an integer of 15 to 1455, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:276, and where b is greater than or equal to a + 14.	
830989	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1909 of SEQ ID NO:277, b is an integer of 15 to 1923, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:277, and where b is greater than or equal to a + 14.	
831134	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1366 of SEQ ID NO:278, b is an integer of 15 to 1380, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:278, and where b is greater than or equal to a + 14.	
831200	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1004 of SEQ ID NO:279, b is an integer of 15 to 1018, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:279, and where b is greater than or equal to a + 14.	
831260	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1178 of SEQ ID NO:280, b is an integer of 15 to 1192, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:280, and where b is greater than or	R15008, R28066, R68324, H20638, N25438, N67982, N67983, N67999, N68004, N68005, N80403, N80423, N80429, N80430, AA024581, AA024582, AA024637, AA862760, AA091142

	equal to $a + 14$.	
831531	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1741 of SEQ ID NO:281, b is an integer of 15 to 1755, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:281, and where b is greater than or equal to $a + 14$.	T66624, R16038, R26139, R26353, H15795, H16285, H21749, H21945, H22698, H23978, H52286, H52523, H60184, H60227, H68044, H81748, H81749, N46859, N47179, N51722, N51808, AA031701, AA031866, AA043760, AA043761, AA081005, AA081148, AA195519, AA470636, AA534463, AA555198, AA631348, AA721036, AA737025, AA761301, AA764993, AA765314, AA765749, AA878422, U47720, C21223
831665	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1079 of SEQ ID NO:282, b is an integer of 15 to 1093, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:282, and where b is greater than or equal to $a + 14$.	
831724	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1542 of SEQ ID NO:283, b is an integer of 15 to 1556, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:283, and where b is greater than or equal to $a + 14$.	R52161, N45179, N68350, N94021, W02782, W24840, W61323, AA907441
831884	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1015 of SEQ ID NO:284, b is an integer of 15 to 1029, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:284, and where b is greater than or equal to $a + 14$.	
831897	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1569 of SEQ ID NO:285, b is an integer of 15 to 1583, where both	AA056348, AA127534

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:285, and where b is greater than or equal to a + 14.	
831922	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1163 of SEQ ID NO:286, b is an integer of 15 to 1177, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:286, and where b is greater than or equal to a + 14.	
831963	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 492 of SEQ ID NO:287, b is an integer of 15 to 506, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:287, and where b is greater than or equal to a + 14.	
832074	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 934 of SEQ ID NO:288, b is an integer of 15 to 948, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:288, and where b is greater than or equal to a + 14.	
832266	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1020 of SEQ ID NO:289, b is an integer of 15 to 1034, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:289, and where b is greater than or equal to a + 14.	T70612, T70879, H13555, H23264, R97792, R97842, N75850, W07434, W19866, N90056, AA043395, AA463232, AA463231
832309	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	

	formula of a-b, where a is any integer between 1 to 3077 of SEQ ID NO:290, b is an integer of 15 to 3091, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:290, and where b is greater than or equal to a + 14.	
832342	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 504 of SEQ ID NO:291, b is an integer of 15 to 518, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:291, and where b is greater than or equal to a + 14.	
832351	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 484 of SEQ ID NO:292, b is an integer of 15 to 498, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:292, and where b is greater than or equal to a + 14.	
832352	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 455 of SEQ ID NO:293, b is an integer of 15 to 469, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:293, and where b is greater than or equal to a + 14.	
832434	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 654 of SEQ ID NO:294, b is an integer of 15 to 668, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:294, and where b is greater than or equal to a + 14.	
832490	Preferably excluded from the present	T86496, H24346, R84505, N26874, N98621,

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1386 of SEQ ID NO:295, b is an integer of 15 to 1400, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:295, and where b is greater than or equal to a + 14.	W04678, W04692, W24267, W93387, W94971, AA036953, AA136869, AA136799, AA147214, AA160413, AA535592, AA931261, AA931403, AA962726, AA992456
832573	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 946 of SEQ ID NO:296, b is an integer of 15 to 960, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:296, and where b is greater than or equal to a + 14.	
832580	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:297, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:297, and where b is greater than or equal to a + 14.	
833394	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 878 of SEQ ID NO:298, b is an integer of 15 to 892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:298, and where b is greater than or equal to a + 14.	
835355	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1610 of SEQ ID NO:299, b is an integer of 15 to 1624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	AA076638, AA916592, AI088936, AI089690

	NO:299, and where b is greater than or equal to a + 14.	
835497	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1955 of SEQ ID NO:300, b is an integer of 15 to 1969, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:300, and where b is greater than or equal to a + 14.	
835728	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1868 of SEQ ID NO:301, b is an integer of 15 to 1882, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:301, and where b is greater than or equal to a + 14.	
835978	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2790 of SEQ ID NO:302, b is an integer of 15 to 2804, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:302, and where b is greater than or equal to a + 14.	
836091	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3845 of SEQ ID NO:303, b is an integer of 15 to 3859, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:303, and where b is greater than or equal to a + 14.	R02093, R02205, R02336, R02439, R19436, R44685, R44685, R72354, H10160, H49884, H49885, N23208, N28789, N29901, N42953, N55093, N77305, N99373, W46396, W46504, AA082311, AA176281, AA176282, AA227971, AA228079, AA234964, AA234145, AA281787, AA281656, AA524468, AA551888, AA631173, AA639499, AA811344, AA830439, AA831974, AA923665, C03439, AA641655, AA091346, AA400968, AA400884
836274	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3364 of SEQ ID NO:304,	T75442, R20393, R43511, R43511, R73650, R73731, R80152, R80886, H97932, H98616, N33018, N71679, N99650, AA001053, AA001089, AA044947, AA044943, AA149057, AA464856, AA427892, AA228265, AA230021, AA482694, AA483691, AA484850, AA513037,

	b is an integer of 15 to 3378, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:304, and where b is greater than or equal to a + 14.	AA516076, AA532381, AA583355, AA618566, AA577028, AA730651, AA730790, AA745667, AA829807, AA923038, AA931937, AA932867, AA934400, AA934413, AA971551, AA971743, AA972772, AA977253, AA992454, AA994794, AI089906, AI094921, D79281, C06099, D44840, C20741, AA283186, AA292346, AA394164
836731	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1000 of SEQ ID NO:305, b is an integer of 15 to 1014, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:305, and where b is greater than or equal to a + 14.	
838014	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2113 of SEQ ID NO:306, b is an integer of 15 to 2127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:306, and where b is greater than or equal to a + 14.	
838874	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 652 of SEQ ID NO:307, b is an integer of 15 to 666, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:307, and where b is greater than or equal to a + 14.	R61165, N44200
839120	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2157 of SEQ ID NO:308, b is an integer of 15 to 2171, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:308, and where b is greater than or equal to a + 14.	T74462, R18264, H23432, AA279685, AA847441, AA904076, AA393782

839611	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 6149 of SEQ ID NO:309, b is an integer of 15 to 6163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:309, and where b is greater than or equal to a + 14.	T93695, T93696, T96161, R32227, R32254, R32304, R33503, R34044, R71178, H93366, N50709, N55039, AA165143, AA199856, AA199927, AA234331, AA262892, AA423987, AA423986, AA525886, AA661602, AA731504, AA741228, AA814795, AA828858, AA829196, AA831198, AA834822, AA865590, AA886436, AA903649, D82270, D82453, D82464, AA642466, AA219620, AA219628, AA400707, AA400674, AA421941, AA633988, AA663219, AA663250, AA665538, AA724260, AI074714, T26891, T26926
840138	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2072 of SEQ ID NO:310, b is an integer of 15 to 2086, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:310, and where b is greater than or equal to a + 14.	
840616	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2149 of SEQ ID NO:311, b is an integer of 15 to 2163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:311, and where b is greater than or equal to a + 14.	
840780	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1383 of SEQ ID NO:312, b is an integer of 15 to 1397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:312, and where b is greater than or equal to a + 14.	
840857	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4092 of SEQ ID NO:313, b is an integer of 15 to 4106, where both	T50389, T50520, T55419, T55495, T55974, T57220, R34591, R34592, R69726, H21148, R85777, R99233, H61311, H62351, H85185, H88299, N23288, N32662, N58504, N78093, N92665, N99611, AA005068, AA007333, AA007334, AA036884, AA044715, AA045458, AA046500, AA045654, AA115936, AA121004,

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:313, and where b is greater than or equal to a + 14.	AA126775, AA133605, AA133606, AA133980, AA181633, AA182611, AA232979, AA233365, AA459953, AA460042, AA282826, AA285050, AA506082, AA558006, AA601060, AA767799, AA804323, AA807029, AA807087, AA825536, AA833810, AA922732, AA928638, AA960990, N56482, N62047, W27456, W26569, AA092778, AA652535, AA065256, AA065257, AA450197, AA452846, AA452986, AA705224, Z19460, AA884767, AA969488, AA977494, AI002996, AI032008, Z28526, D20112, T19336
840862	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 518 of SEQ ID NO:314, b is an integer of 15 to 532, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:314, and where b is greater than or equal to a + 14.	T94528, N40545, N46592, N92934, AA570273, AA873604, AA910827, AA932397, AA971868, AI095210, N56229, AA648290, F20835, AA629912
840864	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1924 of SEQ ID NO:315, b is an integer of 15 to 1938, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:315, and where b is greater than or equal to a + 14.	R40870, R44820, H26640, W78814, W80713, AA195492, AA937549, AI085492, AI094865, AA449317, AA884600, AA909529, AA923452, AA971781, AI084795, AI089007, AA702758, AA702769
840936	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 804 of SEQ ID NO:316, b is an integer of 15 to 818, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:316, and where b is greater than or equal to a + 14.	
840938	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 823 of SEQ ID NO:317, b is an integer of 15 to 837, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:317, and where b is greater than or equal to a + 14.	
841884	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1434 of SEQ ID NO:318, b is an integer of 15 to 1448, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:318, and where b is greater than or equal to a + 14.	
842241	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1479 of SEQ ID NO:319, b is an integer of 15 to 1493, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:319, and where b is greater than or equal to a + 14.	
843712	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 595 of SEQ ID NO:320, b is an integer of 15 to 609, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:320, and where b is greater than or equal to a + 14.	R02291, N94598, W85882, AA255975
844040	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 488 of SEQ ID NO:321, b is an integer of 15 to 502, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:321, and where b is greater than or equal to a + 14.	W24428, AA143434, AA459809
844336	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 2616 of SEQ ID NO:322, b is an integer of 15 to 2630, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:322, and where b is greater than or equal to a + 14.	
844612	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1860 of SEQ ID NO:323, b is an integer of 15 to 1874, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:323, and where b is greater than or equal to a + 14.	
844617	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2311 of SEQ ID NO:324, b is an integer of 15 to 2325, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:324, and where b is greater than or equal to a + 14.	
845251	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:325, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:325, and where b is greater than or equal to a + 14.	T68474, AA159183, AA464447, AA424290, AA424487, AA631793, AA928390, AA946921, AA975194, AA977141, AA430527, AA430612, AA477798
845764	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 230 of SEQ ID NO:326, b is an integer of 15 to 244, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:326, and where b is greater than or equal to a + 14.	
846187	Preferably excluded from the present invention are one or more	

<p>polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2440 of SEQ ID NO:327, b is an integer of 15 to 2454, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:327, and where b is greater than or equal to a + 14.</p>	
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Polynucleotide and Polypeptide Variants

The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, and/or the cDNA sequence contained in a cDNA clone contained in the deposit.

5 The present invention also encompasses variants of the breast, ovarian, breast cancer and/or ovarian cancer polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

10 "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

15 The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the related cDNA contained in a deposited library or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA in the related cDNA contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polypeptides encoded by these nucleic acid molecules are also encompassed by the invention. In another embodiment, the invention encompasses nucleic acid molecules which comprise or alternatively consist of, a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under low stringency conditions, to the nucleotide coding sequence in SEQ ID NO:X, the

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nucleotide coding sequence of the related cDNA clone contained in a deposited library, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

The present invention is also directed to polypeptides which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these polypeptides under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be, for example, an entire sequence referred to in Table 1, an ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of

the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases

were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence in SEQ ID NO:Y or a fragment thereof, the amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237- 245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window

Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results.

5 This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject
10 residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues
15 to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue
20 query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the
25 FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected.
30 Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the

purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, as discussed herein, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., *J. Biotechnology* 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (*J. Biol. Chem.* 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that

"[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

5 Furthermore, as discussed herein, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are
10 removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

 Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptide of the invention of which they are a
15 variant. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

 The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein or fragments thereof, (e.g., including but not limited to fragments encoding a polypeptide
20 having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid
25 molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot
30 analysis for detecting mRNA expression in specific tissues.

 Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed

herein, which do, in fact, encode a polypeptide having a functional activity of a polypeptide of the invention.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA in the related cDNA clone contained in a deposited library, the nucleic acid sequence referred to in Table 1 (SEQ ID NO:X), or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells,

Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30

amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein), an amino acid sequence encoded by SEQ ID NO:X or fragments thereof, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or fragments thereof, is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

Polynucleotide and Polypeptide Fragments

The present invention is also directed to polynucleotide fragments of the breast, ovarian, breast cancer and/or ovarian cancer polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers, for example, to a polynucleotide having a nucleic acid sequence which: is a portion of the cDNA contained in a deposited cDNA clone; or is a portion of a polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited cDNA clone; or is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; or is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; or is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, at least about 100 nt, at least about 125 nt or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from, for example, the sequence contained in the cDNA in a related cDNA clone contained in a deposited library, the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides. These nucleotide fragments have uses that

include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 150, 175, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, and 6151 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the polynucleotide of which the sequence is a portion. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from

about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, and 6151 to the end of the cDNA nucleotide sequence contained in the deposited cDNA clone, or the complementary strand thereto. In this context "about" includes the particularly recited range, or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the cDNA nucleotide sequence contained in the deposited cDNA clone. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these fragments under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, and/or encoded by the cDNA contained in the related cDNA clone contained in a deposited library. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region.

Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, an amino acid sequence from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, 1441-1460, 1461-1480, 1481-1500, 1501-1520, 1521-1540, 1541-1560, 1561-1580, 1581-1600, 1601-1620, 1621-1640, 1641-1660, 1661-1680, 1681-1700, 1701-1720, 1721-1740, 1741-1760, 1761-1780, 1781-1800, 1801-1820, 1821-1840, 1841-1860, 1861-1880, 1881-1900, 1901-1920, 1921-1940, 1941-1960, 1961-1980, and 1981 to the end of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either terminus or at both termini. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, polypeptide fragments of the invention include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in the related cDNA clone contained in a deposited library). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed

herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in deposited cDNA clone referenced in Table 1). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and
5 where n corresponds to the position of an amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides
10 having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y), and/or the cDNA in the related cDNA clone contained in a deposited library, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also
15 encompassed by the invention.

Any polypeptide sequence contained in the polypeptide of SEQ ID NO:Y, encoded by the polynucleotide sequences set forth as SEQ ID NO:X, or encoded by the cDNA in the related cDNA clone contained in a deposited library may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide
20 encoded by a polynucleotide sequence of SEQ ID NO:X, or the cDNA in a deposited cDNA clone may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; <http://www.dnastar.com/>).

Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions,
25 turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that
30 combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Preferred polypeptide fragments of the invention are fragments comprising, or alternatively consisting of, an amino acid sequence that displays a functional activity of the polypeptide sequence of which the amino acid sequence is a fragment.

By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Table 4

Sequence/ Contig ID	Epitope
508678	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 422 as residues: Gln-21 to Arg-43.
508968	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 423 as residues: Thr-1 to Lys-6.
509029	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 424 as residues: Asp-1 to Trp-8, Thr-12 to Cys-19, Pro-41 to Leu-51.
522632	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 426 as residues: Cys-69 to Asn-74, Lys-83 to Gly-89.
524655	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 427 as residues: Tyr-28 to Asn-35, Ile-45 to Lys-55.
525847	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 428 as residues: Lys-27 to Asp-33.
530306	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 429 as residues: Arg-1 to Arg-11, Tyr-21 to His-27.
532818	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 430 as residues: Pro-10 to Thr-21, Asp-32 to Thr-38, Gly-47 to Glu-60.
533385	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 431 as residues: Asn-17 to Trp-22, Pro-34 to Glu-49, His-61 to Ser-71.
533532	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 432 as residues: Glu-29 to Lys-37, Lys-110 to Ile-118, Arg-126 to Cys-135, Lys-157 to Gly-163, Gln-188 to Trp-201, Glu-269 to Thr-278.
534852	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 433 as residues: Gln-1 to Ser-14, Thr-23 to Val-31, Cys-43 to Ala-56, Glu-58 to Ser-96, Gly-101 to Tyr-109, Asn-143 to Tyr-148, Pro-154 to His-164, Ser-195 to Asn-201, Pro-264 to Pro-271.
537910	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 434 as residues: Pro-4 to Ala-11, Pro-110 to Arg-122.
539577	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 436 as residues: Pro-9 to Gln-19.
548595	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 439 as residues: Asp-27 to Asp-33, His-54 to Tyr-59, Ile-91 to Pro-96.
549337	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 440 as residues: Pro-38 to Asp-43, Arg-155 to Phe-162, Pro-164 to Asp-170, Pro-172 to Gly-182.
553091	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 442 as residues: Lys-55 to Lys-62, Gln-67 to Val-76, Lys-101 to Glu-111, Lys-125 to Arg-140, Arg-161 to Arg-166, Gln-171 to Asp-187.
553827	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 443 as residues: Glu-17 to Pro-22, Pro-70 to His-76, Thr-84 to Arg-92, Asp-109 to Tyr-117.
556350	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 444 as residues: Glu-1 to Ser-15, Phe-17 to Pro-22, Lys-116 to Arg-131.
556351	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 445 as residues: Gln-9 to Phe-23, Cys-53 to Ser-64, Glu-86 to Asp-93, Ile-100 to Glu-112, Tyr-124 to Glu-133, Ser-197 to Ser-204, Asn-208 to Glu-214, Lys-228 to Lys-233, Tyr-248 to Lys-259, Pro-330 to Ala-335, Gln-349 to Lys-355, Ala-365 to Glu-374, Ser-376 to Ser-397.
557007	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 446 as residues: Pro-46 to Tyr-54, Pro-81 to Gly-87, Pro-97 to Gly-104, Leu-106 to Asn-116, Asn-129 to Phe-134, Lys-147 to Tyr-158, Ala-192 to Ser-199, Asp-204 to Glu-215, Gly-221 to Ser-232.
558456	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 448 as

	residues: Glu-19 to Tyr-24, Ser-60 to Thr-65, Thr-82 to Pro-88.
558708	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 449 as residues: Arg-13 to Ala-20, Pro-27 to Arg-32, Lys-37 to Glu-62.
574789	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 450 as residues: Gly-16 to Lys-21.
578203	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 451 as residues: Thr-7 to Arg-18.
588869	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 453 as residues: Pro-14 to Ser-19, Glu-55 to Phe-60, Asp-93 to Ser-98, Thr-138 to Tyr-144, Asn-155 to Phe-163, Arg-168 to Ser-175, Gln-205 to Lys-210, Phe-226 to Thr-233.
597076	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 454 as residues: Ser-50 to Gln-56.
598656	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 455 as residues: Ser-85 to Tyr-92, Arg-109 to Lys-114.
614329	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 457 as residues: Arg-59 to Ala-67, Asn-78 to Arg-85.
620956	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 459 as residues: Ala-11 to Gln-16.
621889	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 460 as residues: Ser-84 to Gly-99, Pro-101 to Ser-112.
651784	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 462 as residues: Gly-29 to Gly-35, Ala-37 to Ala-48.
651826	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 463 as residues: Arg-1 to Ser-16, Gln-49 to Lys-60, Glu-77 to Leu-83, Gln-91 to Arg-100, Phe-140 to Ala-154, Asp-214 to Leu-219, Ala-258 to Met-275, Ile-289 to Lys-295, Ala-314 to Glu-320, Arg-327 to Met-332, Thr-383 to Ser-388, Ser-425 to Asp-433.
653282	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 464 as residues: Arg-12 to Ile-19, Glu-23 to Pro-29, Pro-37 to Val-45.
657122	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 465 as residues: Ala-6 to Gly-13, Arg-41 to Thr-47.
661442	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 466 as residues: Arg-6 to Ser-11, Asp-53 to Ser-59, Ala-88 to Ala-104, Thr-114 to Asn-121, Glu-128 to Val-137, Asn-144 to Thr-150, Ser-174 to Asn-180, Gly-203 to Asp-212.
664914	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 467 as residues: Pro-12 to Lys-17.
666654	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 468 as residues: Thr-5 to Leu-10, Pro-13 to Leu-24.
667084	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 469 as residues: Pro-1 to Pro-9, Gly-50 to Ser-55, Gly-80 to Ser-85, Gly-91 to Tyr-96, Arg-144 to Gln-160, Asp-195 to Thr-202, Lys-246 to Glu-252, Met-283 to Glu-288, Glu-292 to Glu-299, Ser-304 to Asn-310, Ala-356 to Tyr-362, Met-387 to Tyr-394, Gln-424 to Thr-431, Ser-450 to Arg-459.
667380	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 470 as residues: Pro-1 to Pro-6, Thr-134 to Gln-140, Tyr-142 to Arg-150.
671315	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 472 as residues: Ala-16 to Gly-21, Glu-28 to Gly-35.
671993	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 473 as residues: Pro-8 to Ser-23.
674618	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 474 as residues: Ile-3 to Ser-11, Arg-24 to Glu-30.
675027	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 475 as residues: His-47 to Ile-52, Ala-71 to Arg-76, Asp-78 to Lys-87.
677202	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 476 as residues: Val-45 to Gly-50, Thr-56 to Glu-64.
678504	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 477 as residues: Arg-7 to Ser-19.

678985	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 478 as residues: Lys-17 to Thr-23, Leu-26 to His-36, His-41 to Pro-56, Ala-60 to Gly-71, Lys-77 to Ser-91, Asp-101 to Lys-109, Asp-200 to Gly-206, Asp-245 to Leu-253, Gln-262 to Phe-274.
682161	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 479 as residues: Arg-5 to Pro-11, Pro-22 to Thr-29, Trp-53 to Arg-62, Pro-69 to Gly-78, Lys-98 to Tyr-103, Glu-144 to His-151, Pro-172 to Leu-178, Gln-193 to Glu-200.
683476	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 480 as residues: Ala-5 to Trp-19.
693589	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 482 as residues: Cys-1 to Arg-13, Pro-15 to Gly-21, Gly-54 to Ser-59, Trp-73 to Lys-78, Ser-90 to Arg-104.
694991	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 483 as residues: Lys-1 to Thr-6, Pro-8 to Gly-19, Val-61 to Arg-66.
698669	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 485 as residues: Pro-31 to His-36, Gly-43 to Tyr-48, Glu-136 to Ser-142, Pro-178 to Arg-183, Pro-273 to Asp-278, Gly-318 to Cys-326.
707357	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 488 as residues: Gly-6 to Arg-21, Arg-89 to Asp-94.
707360	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 489 as residues: Ser-13 to Glu-26, Ser-48 to Val-55, Lys-85 to Thr-91, Asp-115 to Trp-120.
707375	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 490 as residues: Arg-1 to Gly-6, Ala-12 to Arg-19, Arg-34 to Arg-40, Arg-47 to Ala-58, Ser-67 to Thr-80, Ser-109 to Ser-117, Asn-134 to Ser-141, Pro-175 to Arg-181, Lys-212 to Thr-218, Asp-275 to Cys-285.
707754	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 491 as residues: Val-32 to Leu-41, Asn-55 to Arg-63, Pro-104 to Ala-113.
712248	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 493 as residues: Ser-13 to Gly-20, Gln-36 to Ser-41, Pro-44 to Phe-58.
715445	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 494 as residues: Gly-23 to Thr-29, Ser-32 to Val-40, Lys-181 to Ser-188, Glu-197 to Gln-204, Arg-244 to His-249, Ala-253 to Thr-264.
716362	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 495 as residues: Cys-1 to Gly-8, Arg-71 to Ser-77, His-102 to Ser-108.
716835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 496 as residues: Gln-7 to Glu-14, Ala-24 to Arg-41.
717685	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 498 as residues: Gly-1 to Ala-7, His-70 to Gly-76, Gln-130 to Thr-135, Thr-182 to Pro-189, Asn-259 to Leu-267, Glu-280 to Ala-289, Gln-303 to Asn-310.
719755	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 499 as residues: Asp-14 to Pro-25, Pro-59 to Glu-100, Cys-126 to Gly-145, Pro-158 to Lys-164, Lys-176 to Leu-197, Leu-221 to Tyr-238.
720389	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 500 as residues: Thr-13 to Ala-19, Ala-26 to Pro-36, Ser-63 to Gly-68.
720903	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 501 as residues: Asn-6 to Ser-11, Ala-91 to Arg-99, Trp-107 to Tyr-113, Tyr-131 to Met-137, Asp-150 to Val-157.
721562	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 503 as residues: Asp-39 to Ile-45.
722775	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 504 as residues: Pro-34 to Ser-41, Cys-49 to Arg-55, Thr-92 to Ala-98, Thr-160 to Gly-173, Thr-194 to Pro-200, Gly-274 to Trp-282, Pro-285 to Ala-291.
724463	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 505 as residues: Glu-9 to Lys-15, Pro-23 to Tyr-33.
728418	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 507 as residues: Ala-6 to Gln-11, Ser-25 to Ser-30, Lys-63 to Gly-69, Ser-108 to Asp-118, Arg-

	127 to His-132, Asp-156 to Cys-161.
728920	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 508 as residues: Thr-7 to Ala-15.
732958	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 509 as residues: Thr-10 to Ala-15, Pro-63 to Ser-78, Ser-82 to Leu-94.
733134	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 510 as residues: Arg-4 to Gly-24, Lys-47 to Phe-55, Lys-61 to Ala-67, Gly-108 to Thr-114, Pro-184 to Pro-191, Pro-292 to Arg-299, Pro-355 to Glu-392.
734099	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 511 as residues: His-1 to Arg-7, Gln-15 to Ala-23, Met-43 to Gln-55.
738911	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 515 as residues: Arg-4 to Asp-10, Ser-64 to His-75, Pro-127 to Asn-136, Phe-143 to Gln-150.
739226	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 516 as residues: Asn-1 to Thr-7.
739527	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 517 as residues: Gly-1 to Arg-9, Val-28 to Gly-39, Asp-52 to Leu-60, Ala-106 to Trp-117.
744331	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 520 as residues: Ser-17 to Arg-24.
744751	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 521 as residues: Ser-8 to Val-13, Pro-34 to Cys-40, Tyr-48 to Ser-55, Gly-63 to Ser-73.
745750	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 522 as residues: Ser-2 to Glu-17.
746285	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 523 as residues: Lys-87 to Lys-92.
746416	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 524 as residues: Arg-6 to Leu-12, Tyr-18 to Asp-25.
747851	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 525 as residues: Gly-124 to Ser-129, Leu-162 to Gly-167, Val-272 to Ala-278, Lys-293 to Asp-298.
751315	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 527 as residues: Cys-12 to Pro-20.
754634	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 529 as residues: Asp-1 to Thr-10.
756833	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 531 as residues: Thr-36 to Pro-49, Glu-52 to Pro-67.
756878	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 532 as residues: Pro-8 to Lys-15, Gly-69 to Trp-75.
757332	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 533 as residues: Gln-23 to Val-31, Phe-39 to Ile-52.
760835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 534 as residues: Phe-1 to Lys-7, Cys-82 to Ser-90.
761760	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 535 as residues: Arg-34 to Pro-39, Gly-43 to Asp-51, Gln-147 to Arg-153.
762520	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 536 as residues: His-6 to His-11, Ala-13 to Glu-18, Ala-60 to Ser-65, Ile-72 to Ser-77, Gln-95 to Phe-101, Leu-136 to Ser-142.
764461	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 537 as residues: Val-15 to Ala-22, Val-26 to Gly-38.
764517	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 538 as residues: Gly-30 to Lys-36, Gly-94 to Ala-100, Gln-150 to Gly-156, Gln-189 to Leu-195.
765132	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 539 as residues: Asn-80 to Thr-87, Ser-165 to Leu-182, Thr-196 to His-201, Lys-271 to His-279, Asp-286 to Gly-292, Tyr-294 to Leu-302.
765667	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 540 as residues: Pro-14 to Pro-21, Pro-30 to Pro-36.

767113	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 541 as residues: Ala-62 to Pro-73, Pro-75 to Thr-83, Thr-110 to Phe-115, Glu-142 to Asp-150, Gln-158 to Ser-167, Glu-182 to Thr-187, Ser-190 to Asp-204.
767204	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 542 as residues: Ala-22 to Met-29, Arg-45 to Phe-56, Asp-63 to Asp-71, Gly-81 to Ala-88, Gln-155 to Trp-162.
767962	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 544 as residues: Glu-126 to Gly-132, Asn-146 to Ser-158, Phe-179 to Leu-188.
768040	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 545 as residues: Pro-24 to Trp-32, Val-51 to Arg-62, Gly-84 to Asp-93, Asp-108 to Asn-120, Glu-150 to Val-158, Gly-169 to Gly-175.
769956	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 546 as residues: Pro-1 to Arg-6.
770133	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 547 as residues: Glu-1 to Ser-6.
771964	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 549 as residues: Pro-8 to Gly-15, Thr-26 to Phe-32, Thr-102 to Ser-109, Ala-112 to Thr-118, His-130 to Glu-152, Ser-161 to Ala-170, Ser-204 to His-209, Gly-221 to Ser-229, Ser-233 to Ala-240, Glu-242 to Pro-247, Leu-251 to Gln-258, Leu-278 to Leu-285, Thr-333 to Glu-338.
773387	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 551 as residues: Lys-36 to Lys-45, Ala-59 to Arg-67, Cys-99 to Arg-108, Ala-115 to Cys-125, Arg-143 to Arg-153.
773827	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 552 as residues: Pro-1 to Ala-15, Ser-72 to His-79, Gly-89 to Tyr-105, Lys-179 to Lys-184, Arg-246 to Asp-251, Glu-302 to Lys-309, Ser-329 to Phe-341.
774108	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 553 as residues: Ala-1 to Gly-21, Pro-28 to Leu-39, Pro-48 to Asp-62, Arg-71 to Arg-78.
775339	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 555 as residues: Asp-6 to Thr-13, Asp-24 to Met-30.
775582	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 556 as residues: Gly-1 to Asn-12, Ser-69 to Glu-77.
777809	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 558 as residues: Arg-15 to Gly-25.
778927	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 559 as residues: Ala-74 to Ser-82, Asn-109 to Ala-124, Ser-147 to Ile-152, Pro-188 to Gly-194, Arg-290 to Pro-299, Tyr-307 to Glu-319, Tyr-341 to Ile-346, Lys-423 to Ser-441, Gln-452 to Glu-465.
779262	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 560 as residues: Arg-5 to Ile-24, Gly-35 to Trp-40, Glu-42 to Thr-48, Lys-76 to Gly-95.
780149	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 562 as residues: Gly-13 to Gln-18, Pro-71 to Glu-89, Ile-134 to Asp-139, Pro-232 to Met-240.
780583	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 563 as residues: Asn-58 to Thr-64, Ile-72 to Ser-78, Gly-119 to Lys-128.
780960	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 564 as residues: Ala-7 to Ile-14, Lys-27 to Asp-35, Thr-63 to Leu-73.
781469	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 565 as residues: Pro-1 to Ala-12, Arg-27 to Gln-45, Arg-57 to Gln-64, Lys-74 to Asp-96.
781771	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 567 as residues: Glu-38 to Leu-52, Glu-64 to Lys-72, Asn-92 to Ala-102, Ala-104 to Asp-119, Pro-121 to Pro-130, Ser-165 to Ser-173.
782033	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 568 as residues: Ala-1 to Gly-19, Gln-41 to Gly-46.
782105	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 569 as residues: Leu-13 to Gly-34, Arg-77 to Pro-85, Lys-129 to Arg-135.
782122	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 570 as

	residues: Pro-1 to Arg-6, Ala-102 to Ala-108, Pro-148 to Asp-158, Gly-164 to Ala-171, Pro-223 to Asn-231, Pro-272 to Ser-282, Ala-294 to Pro-310, Pro-322 to Arg-327.
783245	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 572 as residues: Leu-90 to Arg-97, Ala-107 to Pro-113.
783247	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 573 as residues: Ser-2 to Leu-8.
783413	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 574 as residues: Lys-33 to Val-39.
784407	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 575 as residues: Gly-28 to Val-36.
784548	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 576 as residues: Trp-1 to Pro-9, Pro-15 to Gln-24, Pro-52 to Thr-57.
785677	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 578 as residues: Gly-7 to Gly-14.
786238	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 579 as residues: Gly-1 to Gly-8.
786389	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 580 as residues: Ser-2 to Arg-16, Gly-34 to Glu-44, Arg-62 to Gln-69, Pro-102 to Ile-108, Asp-187 to Thr-193, Leu-203 to Pro-213.
786929	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 581 as residues: Pro-2 to Trp-7, Tyr-36 to Tyr-43.
786932	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 582 as residues: Ser-18 to His-30, Thr-39 to Arg-51, Leu-59 to Thr-66, Pro-131 to Lys-136, Pro-149 to Ser-157.
787078	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 583 as residues: Glu-20 to Pro-26.
787283	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 585 as residues: Glu-7 to Arg-13, Gln-26 to Arg-34.
788988	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 587 as residues: Pro-41 to Tyr-50, Thr-70 to Lys-75.
789092	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 588 as residues: Thr-27 to Ala-34, Leu-41 to Glu-48, Glu-76 to Asn-87, Asn-110 to Leu-118, Gly-125 to Lys-133.
789298	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 589 as residues: Arg-1 to Ser-14, Glu-56 to Gly-61, Ala-92 to Gln-98, Glu-134 to Val-154.
789718	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 591 as residues: Cys-17 to Ala-24.
790285	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 594 as residues: Thr-11 to Leu-18, Leu-22 to Val-31, Trp-33 to Lys-49, Ser-63 to Glu-72, Cys-80 to Ala-91, Pro-97 to His-116.
790509	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 595 as residues: Ser-6 to His-20, Leu-22 to Gly-32, Lys-103 to Arg-111, Ser-125 to Gly-130, Glu-204 to His-210, Thr-213 to His-219, Pro-222 to Asp-244, Ser-250 to Glu-258, Arg-263 to Arg-268.
790775	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 596 as residues: Arg-42 to Asp-48, Cys-79 to Thr-85, Leu-113 to Ser-123.
790888	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 597 as residues: Pro-14 to Asp-19, Asp-40 to Leu-45, Ser-53 to Val-58, Leu-81 to Tyr-91.
791506	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 598 as residues: Arg-1 to Gly-9, Asp-19 to His-25, Gly-51 to Glu-61.
792002	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 601 as residues: Arg-1 to Gly-6, Val-22 to Pro-35, Val-106 to Ile-112, His-118 to Gln-124, Ser-132 to Leu-145, Asn-164 to Asn-170, Arg-187 to Tyr-192.
792291	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 602 as residues: Pro-14 to Arg-31.
792371	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 603 as

	residues: Gly-37 to Gly-52, Pro-63 to Gly-69, Ser-74 to His-81, Ser-94 to Thr-105, Val-109 to Thr-114, Phe-165 to Ser-181, Ala-191 to Asp-196, Asn-209 to Ser-216.
792660	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 604 as residues: Thr-11 to Arg-16, Asn-78 to Asp-84.
792782	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 605 as residues: Ala-65 to Gly-81.
792890	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 606 as residues: Pro-26 to His-31, Arg-34 to Ser-44, Pro-59 to Ser-71, Leu-77 to Gly-83.
792931	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 607 as residues: Pro-3 to His-12.
792943	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 608 as residues: Lys-3 to Tyr-9, Gly-15 to Thr-22, Leu-36 to Asp-41, Leu-67 to Lys-76, Asp-86 to Ser-93, Tyr-174 to Asp-184, Leu-255 to Glu-260, Ile-331 to Val-337.
793446	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 611 as residues: His-1 to Gly-12.
793639	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 612 as residues: Arg-6 to Arg-13, Pro-47 to Val-52, Gln-57 to Arg-65, Arg-72 to Glu-78, Asp-117 to Thr-124, Phe-132 to His-137.
794213	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 613 as residues: Tyr-1 to Trp-9, Thr-44 to Leu-49.
795955	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 615 as residues: Lys-60 to Lys-65, Lys-99 to Ala-104.
796555	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 617 as residues: Ser-1 to Gly-10, Glu-90 to Gly-97, Asn-185 to Arg-197, Pro-202 to Arg-211.
796675	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 618 as residues: Ser-35 to Gly-40, Ser-103 to His-109, Tyr-151 to Gly-159, Pro-216 to Glu-224, Asn-249 to Trp-258, Pro-278 to Glu-284.
796743	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 619 as residues: Asn-1 to Gly-6, Asn-100 to Glu-106, Gln-108 to Asp-116, Asp-146 to Thr-151, Thr-191 to Glu-198.
796792	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 620 as residues: Asn-23 to Gly-28, Cys-41 to Asp-47, Gln-82 to Glu-88.
799668	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 621 as residues: Gly-2 to Arg-10, Ile-27 to Pro-33.
799669	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 622 as residues: Gly-1 to Ser-12.
799673	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 623 as residues: Gly-1 to Ala-14, Leu-38 to Pro-46.
799674	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 624 as residues: Pro-39 to Pro-45.
799678	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 625 as residues: Lys-54 to Ser-60, Tyr-86 to His-93.
799728	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 626 as residues: Trp-7 to Gln-19.
799748	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 627 as residues: Glu-7 to Arg-12, Lys-62 to His-68.
799760	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 628 as residues: Ile-15 to Trp-22.
800296	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 630 as residues: Asn-19 to Thr-39, Glu-42 to Ile-48, Arg-55 to Asp-66, Ile-130 to Arg-135, Lys-149 to Ala-156, Glu-166 to Leu-176, Met-213 to Lys-219, Pro-233 to Pro-248, Lys-258 to Lys-263.
800327	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 631 as residues: Arg-13 to Gly-19, Lys-32 to Glu-39, Lys-94 to Trp-100, Asn-102 to Asp-108, Ala-117 to Leu-129.
800816	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 632 as

	residues: Lys-1 to Ile-11, Gln-36 to Leu-46.
800835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 633 as residues: Trp-1 to Gln-11, Gly-37 to Gln-50, Ser-109 to Gln-114, Glu-146 to Leu-155, Glu-175 to Gly-180, Thr-188 to Ser-200.
805429	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 634 as residues: Pro-6 to Ser-51, Gln-100 to Glu-107.
805458	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 635 as residues: Glu-57 to Ser-62, Thr-102 to Ser-120.
805478	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 636 as residues: Glu-31 to Glu-37, Pro-47 to Ser-52, Asn-57 to Asn-66.
805805	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 637 as residues: Arg-1 to Cys-16, Tyr-59 to Lys-68, Glu-76 to Arg-82.
806486	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 638 as residues: Phe-1 to Val-6, Pro-11 to Gly-18.
806498	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 639 as residues: Pro-6 to Ser-17, Arg-81 to Thr-88, Arg-198 to Val-203, Arg-285 to Arg-296, Gln-302 to Ser-361, Leu-399 to Ser-407.
810870	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 641 as residues: Val-12 to Ile-21.
811730	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 642 as residues: Arg-33 to Arg-40.
813262	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 645 as residues: Gly-31 to Asp-51, Cys-68 to Val-81, Leu-85 to Cys-92.
815637	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 646 as residues: Arg-13 to Asp-19, Ser-80 to Gly-91, Pro-99 to Ser-111.
815853	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 647 as residues: Cys-25 to Ser-31, Gln-63 to Asp-73, Arg-98 to Gly-106, Pro-120 to Arg-125, Leu-136 to Asp-141, Gly-155 to Glu-170, Phe-179 to Gly-186.
815999	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 648 as residues: Asp-1 to Asp-10, Arg-19 to Glu-28, Gly-86 to Leu-93, Arg-113 to His-118.
823427	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 649 as residues: Pro-16 to Cys-27, Arg-70 to Arg-76.
823704	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 650 as residues: Val-29 to Lys-34, Arg-58 to His-63, Gln-87 to Lys-97, Arg-195 to Ser-200.
824798	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 651 as residues: Thr-28 to His-34.
825018	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 652 as residues: Gln-1 to Asn-11, Leu-19 to Thr-24, Lys-47 to Arg-55, Lys-94 to Asp-99, Ala-101 to Arg-107, Ala-137 to Tyr-146, Gln-150 to Ser-163, Gly-169 to Lys-175, Thr-182 to Ala-189, Glu-249 to Ser-258, Pro-266 to Tyr-275, Tyr-285 to Gly-298, Asp-302 to Gln-315, Tyr-318 to Thr-325, Gln-332 to Ala-359, Ser-372 to Phe-384, Leu-390 to Ala-399, Ala-428 to Arg-437.
825787	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 654 as residues: Pro-21 to Leu-28, Arg-40 to Ile-49, Asp-84 to Asn-93, Arg-124 to Asn-130, Gly-140 to Asn-145, Leu-187 to Gln-196, Pro-208 to Asp-213, Arg-244 to Asp-252, Ile-325 to Gln-336, Glu-372 to Ala-379, Asn-435 to Leu-446, Ala-460 to Arg-467, Val-500 to Asp-506, Lys-524 to Asn-533, Thr-592 to Lys-598, Asp-648 to Ser-656.
826116	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 655 as residues: Glu-20 to Cys-35.
826147	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 656 as residues: Lys-18 to Leu-24.
827586	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 658 as residues: Ser-7 to Gly-14, Leu-22 to Ala-28, Thr-57 to Ser-62.
827735	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 660 as residues: Pro-2 to Ser-12, Gln-25 to Glu-31, Val-40 to Arg-45.
827740	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 661 as

	residues: Ile-22 to Lys-28.
827808	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 662 as residues: Glu-2 to Gln-13, Gln-20 to Gly-29, Arg-32 to Cys-47, Pro-54 to Trp-61, Thr-73 to Gln-91, Gly-96 to Ser-103.
828357	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 664 as residues: Gly-1 to Gly-10, Val-25 to Glu-32, His-67 to Arg-73.
828612	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 666 as residues: Asp-25 to Gln-31, Asp-36 to Tyr-41, Gln-43 to Thr-48, Lys-71 to Thr-76.
828647	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 667 as residues: Ser-2 to Ser-8, Arg-61 to Gln-74, Ser-192 to Asn-202, Gln-229 to Lys-236, Gly-281 to Gly-292, Glu-333 to Ala-345, Ala-352 to Gln-358, Glu-360 to Leu-366, Asp-443 to Ser-449, Glu-452 to Glu-459, Asp-485 to Thr-492, Ala-510 to Gln-516, Ala-545 to Ala-552, Leu-560 to Thr-566, Glu-586 to Ala-592, Asp-601 to Gln-607, Leu-609 to Leu-620.
828698	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 668 as residues: Pro-28 to Ser-43, Pro-45 to Ala-50, His-58 to Gln-63.
828962	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 669 as residues: Ala-42 to Gly-49, Thr-54 to Cys-63.
829282	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 671 as residues: Ser-7 to Gln-12, Gly-25 to Gly-31, Gly-71 to Gly-84, Leu-147 to Glu-164, Trp-172 to Leu-180.
829368	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 672 as residues: Glu-1 to Tyr-7, Pro-13 to Glu-24, Arg-31 to Ile-39, Gln-59 to Lys-65, His-67 to Leu-74.
829751	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 673 as residues: Ala-29 to Arg-45, Ser-48 to Glu-59, Lys-73 to Trp-79, Ala-100 to Ser-109.
829934	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 675 as residues: Arg-1 to Arg-6, Ser-46 to Asp-71, Glu-76 to Glu-90, Gln-107 to Tyr-118, Ser-124 to Asp-131, Glu-163 to Asp-170, Ala-239 to Asp-245, Asp-262 to Arg-268, Gln-276 to Asp-283, Arg-293 to Lys-300, Ser-307 to Glu-313, Phe-346 to Phe-351, Phe-361 to Ala-373.
829951	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 677 as residues: Thr-21 to Lys-28.
830173	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 678 as residues: Gly-51 to Asn-68, Thr-75 to Lys-82, Ala-86 to Ala-97, Asn-99 to Arg-106, Leu-121 to Phe-126, Ala-155 to Ser-163, Asp-175 to Asp-180, Ala-184 to Phe-196, Leu-204 to Asn-214, Asp-219 to Gln-232, Leu-269 to Arg-274, Pro-392 to Pro-400, Thr-430 to Asn-437, Tyr-472 to Gln-477, Leu-483 to Gln-499, Asn-516 to Gln-524, Ser-533 to Gln-546, Lys-562 to Glu-576, Leu-589 to Ala-594, Asp-624 to Ala-633, Ile-741 to Asp-746, Val-817 to Lys-839, Tyr-872 to Lys-878, Thr-929 to Asp-940.
830365	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 680 as residues: Trp-36 to Glu-41, Asp-71 to Arg-76, Asn-80 to Gly-87, Arg-103 to Pro-115.
830456	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 681 as residues: Leu-48 to Cys-54.
830549	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 682 as residues: Ser-1 to Pro-24, Pro-40 to Thr-50, Glu-62 to Gly-83, Arg-103 to Leu-108, Ser-141 to Lys-146, Lys-184 to Ser-190.
830602	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 683 as residues: Arg-53 to Thr-63, Ile-100 to Lys-108.
830610	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 684 as residues: Pro-27 to Cys-32, Ala-61 to Gly-70, Pro-76 to Gly-85, Met-115 to Gly-120, Glu-162 to Lys-171, Pro-222 to Tyr-228, Glu-242 to Thr-248, Lys-261 to Gly-269.
830644	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 685 as residues: Ile-1 to Ser-10.
830707	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 686 as residues: Asn-34 to Leu-53, Gln-61 to Leu-67.

830709	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 687 as residues: Arg-13 to Gln-18, Pro-22 to Ala-40, Ala-66 to Asp-84, Glu-94 to Arg-101.
830733	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 688 as residues: Glu-1 to Asp-8.
830855	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 690 as residues: Ser-1 to His-6.
830949	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 691 as residues: Arg-5 to Arg-12, Gly-25 to Trp-30, Thr-77 to Trp-96, Thr-101 to Glu-106, Gly-109 to Arg-127.
830965	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 692 as residues: Leu-24 to Arg-56, Pro-83 to Arg-90, Ile-110 to Ile-115, Lys-123 to Val-136.
830973	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 693 as residues: Ser-1 to Asn-7, Tyr-13 to Asp-23.
830989	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 695 as residues: Cys-2 to Ser-16, Glu-55 to Lys-61, Pro-83 to Leu-88, Ser-135 to Pro-148, Val-152 to Arg-163, Pro-223 to Thr-230, Ala-242 to Val-253, Arg-258 to Glu-274, Gly-290 to Asp-300, Lys-337 to Asn-345, Asp-373 to Ala-398, Gly-401 to Lys-406, Gln-410 to Ala-430, Pro-433 to Gln-460.
831134	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 696 as residues: Ala-19 to His-24.
831200	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 697 as residues: Trp-1 to Gly-6.
831531	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 699 as residues: Ser-94 to Asn-116, Glu-139 to Asp-155, Tyr-190 to Leu-195, Ile-230 to Ile-235, Ser-309 to Glu-317.
831665	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 700 as residues: Leu-4 to Trp-12.
831724	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 701 as residues: Pro-26 to Lys-32.
831884	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 702 as residues: Pro-46 to Ala-52, Thr-68 to Trp-86, Arg-91 to Arg-96, Lys-127 to Asp-141.
831897	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 703 as residues: Pro-10 to Ser-20, Val-73 to Ser-78, Asp-123 to Glu-134, Leu-138 to Val-149, Ala-181 to Ala-187, Thr-189 to Val-196, Arg-213 to Gln-224.
831922	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 704 as residues: Leu-32 to Asp-37, Ile-43 to Asn-49.
832266	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 707 as residues: Ala-73 to Arg-79.
832309	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 708 as residues: Val-10 to Gly-15, Ser-98 to Thr-105.
832342	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 709 as residues: Pro-9 to Trp-16, Thr-66 to Ser-72.
832351	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 710 as residues: Asp-16 to Val-21, Leu-54 to Asp-71.
832352	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 711 as residues: Asp-16 to Val-21, Leu-33 to Asp-50.
832434	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 712 as residues: Tyr-15 to Glu-23, Ser-46 to Arg-51, Gln-56 to Trp-61, Pro-79 to Lys-86.
832490	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 713 as residues: Arg-16 to Gly-23, Ala-37 to Asp-46, Asp-91 to Asp-97.
832573	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 714 as residues: Ala-9 to Gln-16, Glu-21 to Arg-27, Gly-66 to Pro-72.
833394	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 716 as residues: Glu-1 to Gly-6, Asp-12 to Gly-22, Ile-28 to Gln-33, Cys-86 to Gly-92, Gly-96 to Ile-105.
835355	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 717 as

	residues: Glu-8 to Ser-15, Gly-42 to Leu-49, Pro-73 to Gly-79, Tyr-82 to Arg-87, Ser-109 to Gly-118, Glu-122 to Ile-128, Asp-132 to Gly-137, Asp-146 to Arg-151, Pro-153 to Lys-158, Gly-191 to His-197, Tyr-210 to Ser-218, Lys-234 to Gly-239, Ala-246 to Ala-252, His-257 to Pro-268, Ser-274 to Gly-280, Pro-316 to Tyr-323, Ile-358 to Leu-363, Gln-375 to Tyr-381, Gln-390 to Tyr-397, Gln-418 to Cys-430.
835497	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 718 as residues: Glu-141 to Pro-151, Asp-179 to Glu-184, Gly-214 to Ser-219, Thr-226 to Tyr-231, Thr-239 to Gly-248, Pro-281 to Gly-297, Pro-326 to Arg-336, Gln-408 to Asp-416.
835978	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 720 as residues: Trp-25 to Val-31.
836274	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 722 as residues: Ser-1 to Glu-9.
836731	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 723 as residues: Lys-15 to Glu-22, Gly-25 to Ala-34, Glu-75 to Gly-81, Gln-91 to Val-100, Pro-146 to Glu-155, Gln-161 to Phe-167, Asn-170 to Gly-178.
838014	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 724 as residues: Arg-1 to Pro-10, Asp-170 to Pro-176, Arg-203 to Tyr-212, Gly-228 to Lys-235.
838874	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 725 as residues: Gln-30 to Gln-45.
839120	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 726 as residues: Thr-22 to Arg-27, Arg-69 to Gly-75, Leu-77 to Pro-85.
839611	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 727 as residues: Asp-12 to Thr-17.
840138	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 728 as residues: Ser-1 to Thr-10.
840616	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 729 as residues: Lys-93 to Gly-99, Glu-144 to Leu-160, Ser-265 to Asp-270, Thr-382 to Gln-396, Val-512 to Val-517, Glu-519 to Asp-535.
840780	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 730 as residues: Leu-8 to Gly-14, Pro-151 to Glu-157.
840857	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 731 as residues: Gln-7 to Glu-22, Ala-27 to Arg-46, Ser-138 to Lys-147, Lys-158 to Pro-163, Asn-171 to Glu-187, Glu-202 to Val-208, Glu-234 to Gly-240, Ser-253 to Lys-260, Gln-272 to Pro-279, Arg-292 to Glu-307, Arg-310 to Arg-317, Asp-342 to Gly-351, Pro-367 to Gly-375, Pro-378 to Arg-388, Leu-425 to Ala-447, Arg-536 to Asp-544, Lys-551 to Lys-561, Val-599 to Asp-604, Ser-622 to Ala-630, Pro-653 to Phe-659, Thr-666 to Ile-673, Pro-699 to Phe-705, Asn-709 to Gly-719, Ala-725 to Phe-737.
840862	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 732 as residues: Arg-2 to Pro-12, Lys-32 to Asn-37, His-75 to Asn-82.
840864	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 733 as residues: Pro-17 to Arg-30, Cys-34 to Gly-40, Met-74 to Glu-81, Pro-106 to Asp-111, Val-136 to Cys-147, Asn-192 to Asp-198.
840938	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 735 as residues: Ser-140 to Thr-148, Thr-194 to Lys-202.
841884	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 736 as residues: Thr-34 to Glu-47.
842241	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 737 as residues: Thr-92 to Lys-101, Glu-134 to Thr-142, Glu-149 to Lys-155, Trp-179 to Ser-187, Thr-205 to Arg-211, Ser-218 to Tyr-225, Asp-283 to Gln-290, Glu-292 to Ile-302, Asn-304 to Met-315.
843712	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 738 as residues: Arg-10 to Asn-16, Ala-59 to Pro-67.
844040	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 739 as residues: Phe-59 to Glu-68, Lys-105 to Gly-111.
844617	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 742 as

	residues: Arg-1 to Lys-7.
846187	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 745 as residues: Gly-8 to Gly-14, Gly-41 to Glu-48, Glu-54 to Lys-74, Glu-87 to Arg-98, Thr-158 to Asn-166, Gly-247 to Ser-254, Gly-257 to Arg-277, Ala-437 to Ser-444, Lys-505 to Arg-510, Phe-519 to Tyr-525, Lys-531 to Pro-538, Gly-562 to Leu-571, Phe-606 to Val-613, Val-692 to Ala-697, Ser-705 to Leu-715, Leu-742 to Cys-747.
HANGA53R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 749 as residues: Arg-4 to Ser-9.
HAHCP93R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 752 as residues: Ser-1 to Ser-12, Thr-23 to Arg-28.
HBGAA76R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 753 as residues: Ser-4 to Ser-11, Pro-27 to Asn-37.
HTXPI29R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 756 as residues: Thr-17 to Leu-24, Thr-57 to Tyr-67, Leu-92 to Phe-102, Asn-128 to Gln-134.
HBGAA54R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 760 as residues: Arg-62 to Leu-70, Ile-74 to Arg-79.
HDPJR77R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 763 as residues: Glu-7 to Lys-22, Thr-33 to Glu-39, Lys-69 to Glu-76, Asp-84 to Tyr-90.
HTTIO41R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 764 as residues: Val-17 to Ser-22, Arg-41 to Glu-46, Lys-50 to Pro-75, Ser-92 to Pro-100.
HDPUL86R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 767 as residues: Lys-7 to Gly-13.
HTXNT16R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 768 as residues: Leu-67 to Asn-72, Thr-102 to Phe-111, Gly-127 to Gln-135.
HLXNA54R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 770 as residues: Gln-1 to Glu-6, Pro-23 to Trp-31, Arg-46 to Trp-51.
H2LAX93R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 772 as residues: Glu-3 to Gln-10.
HWAFW10R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 773 as residues: Glu-13 to Asp-22, His-34 to Trp-40, Arg-69 to Lys-75.
HBGDD17R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 775 as residues: Arg-23 to Thr-28, Pro-40 to Glu-51, Ala-62 to His-68.
H2CBB43R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 778 as residues: Asp-90 to Asp-95, Arg-106 to Thr-117.
H2CBQ77R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 779 as residues: Asp-11 to Gly-16, Gln-19 to Tyr-24, Pro-34 to Gly-46.
HOEMK06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 781 as residues: Pro-1 to Gln-14.
HCHAG30R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 783 as residues: Gly-1 to Trp-7.
HAEAI26R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 788 as residues: Lys-32 to Val-40, Arg-43 to Pro-51.
H2CBN76R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 791 as residues: Ala-17 to Leu-22, Thr-72 to Lys-77.
HAGFX49R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 792 as residues: Ala-10 to Leu-15, His-64 to Cys-71.
HTXKR32R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 794 as residues: Ser-2 to Gly-12, Glu-57 to Val-65.
H6EAF46R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 796 as residues: Arg-11 to Ser-21.
H2LAK40R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 798 as residues: Glu-11 to Lys-20, Pro-22 to Arg-28.
H2LAY71R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 799 as residues: Arg-26 to Leu-36, Gln-82 to Asp-101, Arg-103 to Arg-108, Arg-113 to Arg-131.
HASAW80R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 803 as

	residues: Gly-1 to Arg-6, Ala-19 to Pro-27, Gly-34 to Phe-40.
HCHAF25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 804 as residues: Ser-30 to Thr-40, Leu-78 to Val-85, Asp-92 to Ala-97.
HLTHH84R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 805 as residues: Glu-2 to Ala-8.
HADDC09R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 808 as residues: Leu-3 to Gly-9, Thr-20 to Gly-29.
HAQA110R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 811 as residues: Gly-1 to Lys-21.
HBGBT78R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 814 as residues: Asn-1 to Lys-22.
HBGCB06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 815 as residues: Phe-1 to Phe-15.
HCHMW05R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 823 as residues: Pro-6 to Ser-11.
HODFW25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 829 as residues: Ser-1 to Thr-8, Glu-17 to Ala-32, Arg-39 to Trp-47.
HOEMQ91R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 830 as residues: Arg-8 to Ser-13.
HOGBG56R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 831 as residues: Lys-20 to Arg-25.

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide sequence shown in SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or encoded by a polynucleotide that hybridizes to the complement of an epitope encoding sequence of SEQ ID NO:X, or an epitope encoding sequence contained in
5 the deposited cDNA clone under stringent hybridization conditions, or alternatively, under lower stringency hybridization conditions, as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide
10 sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to this complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions, as defined supra.

The term "epitopes," as used herein, refers to portions of a polypeptide having
15 antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example,
20 by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but
25 does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

30 In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at

least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., *Cell* 37:767-778 (1984); Sutcliffe et al., *Science* 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., *Proc. Natl. Acad. Sci. USA* 82:910-914; and Bittle et al., *J. Gen. Virol.* 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., *J. Gen. Virol.*, 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice

are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention, and immunogenic and/or antigenic epitope fragments thereof can be fused to other polypeptide sequences. For example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof) resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995).

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, may be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for

immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).)

5 Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., *Cell* 37:767 (1984).)

15 Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

 Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., *Proc. Natl. Acad. Sci. USA* 88:8972- 897 (1991)). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto 20 Ni²⁺ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

 Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., 30

Curr. Opin. Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

As discussed herein, any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

In certain preferred embodiments, proteins of the invention comprise fusion proteins wherein the polypeptides are N and/or C- terminal deletion mutants. In preferred embodiments, the application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences encoding polypeptides having the amino acid sequence of the specific N- and C-terminal deletions mutants. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

10 **Vectors, Host Cells, and Protein Production**

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include,

but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells.

5 Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-
10 3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1,
15 pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in
20 many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid
25 extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention can also be recovered from: products purified
30 from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast,

higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O₂. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O₂. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to

the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., Nature, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the

polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

Non-naturally occurring variants may be produced using art-known mutagenesis techniques, which include, but are not limited to oligonucleotide mediated mutagenesis, alanine scanning, PCR mutagenesis, site directed mutagenesis (*see, e.g., Carter et al., Nucl. Acids Res. 13:4331 (1986); and Zoller et al., Nucl. Acids Res. 10:6487 (1982)*), cassette mutagenesis (*see, e.g., Wells et al., Gene 34:315 (1985)*), restriction selection mutagenesis (*see, e.g., Wells et al., Philos. Trans. R. Soc. London SerA 317:415 (1986)*).

The invention additionally, encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH_4 ; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased

solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200; 500; 1000; 1500; 2000; 2500; 3000; 3500; 4000; 4500; 5000; 5500; 6000; 6500; 7000; 7500; 8000; 8500; 9000; 9500; 10,000; 10,500; 11,000; 11,500; 12,000; 12,500; 13,000; 13,500; 14,000; 14,500; 15,000; 15,500; 16,000; 16,500; 17,000; 17,500; 18,000; 18,500; 19,000; 19,500; 20,000; 25,000; 30,000; 35,000; 40,000; 50,000; 55,000; 60,000; 65,000; 70,000; 75,000; 80,000; 85,000; 90,000; 95,000; or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik *et al.*, *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a

reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-

304 (1992); Francis *et al.*, *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($\text{ClSO}_2\text{CH}_2\text{CF}_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each protein of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992).

The breast/ovarian cancer antigen polypeptides of the invention may be in monomers or multimers (*i.e.*, dimers, trimers, tetramers and higher multimers). Accordingly, the present

invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers,
5 or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or an amino acid sequence encoded by SEQ ID NO:X, and/or an amino acid sequence encoded by the cDNA in a related cDNA clone
10 contained in a deposited library (including fragments, variants, splice variants, and fusion proteins, corresponding to any one of these as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the
15 invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at
20 least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric
25 multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example,
30 homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention

contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, or contained in a polypeptide encoded by SEQ ID NO:X, and/or by the cDNA in the related cDNA clone contained in a deposited library). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the

invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide

components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG,

IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')₂, Fd, single-chain
5 Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable
10 region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human
15 immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of
20 a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553
25 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid
30 residues. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that

specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., *Blood* 92(6):1981-1988 (1998); Chen et al., *Cancer Res.* 58(16):3668-3678 (1998); Harrop et al., *J. Immunol.* 161(4):1786-1794 (1998); Zhu et al., *Cancer Res.* 58(15):3209-3214 (1998); Yoon et al., *J. Immunol.* 160(7):3170-3179 (1998); Prat et al., *J. Cell. Sci.* 111(Pt2):237-247 (1998); Pitard et al., *J. Immunol. Methods* 205(2):177-190 (1997); Liautard et al., *Cytokine* 9(4):233-241 (1997); Carlson et al., *J. Biol.*

Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

Antibodies of the present invention may be used, for example, but not limited to, to
5 purify, detect, and target the polypeptides of the present invention, including both in vitro and
in vivo diagnostic and therapeutic methods. For example, the antibodies have use in
immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the
present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory
Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference
10 herein in its entirety).

As discussed in more detail below, the antibodies of the present invention may be
used either alone or in combination with other compositions. The antibodies may further be
recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically
conjugated (including covalently and non-covalently conjugations) to polypeptides or other
15 compositions. For example, antibodies of the present invention may be recombinantly fused
or conjugated to molecules useful as labels in detection assays and effector molecules such as
heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO
92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

The antibodies of the invention include derivatives that are modified, i.e., by the
20 covalent attachment of any type of molecule to the antibody such that covalent attachment
does not prevent the antibody from generating an anti-idiotypic response. For example, but
not by way of limitation, the antibody derivatives include antibodies that have been modified,
e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by
known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other
25 protein, etc. Any of numerous chemical modifications may be carried out by known
techniques, including, but not limited to specific chemical cleavage, acetylation, formylation,
metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or
more non-classical amino acids.

The antibodies of the present invention may be generated by any suitable method
30 known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various
procedures well known in the art. For example, a polypeptide of the invention can be
administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to

induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by

fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')₂ fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). F(ab')₂ fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any

desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')₂ fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entirety).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology* 203:46-88 (1991); Shu et al., *PNAS* 90:7995-7999 (1993); and Skerra et al., *Science* 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Gillies et al., (1989) *J. Immunol. Methods* 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., *Nature* 332:323 (1988), which are incorporated herein by reference in their entirety.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489-498 (1991); Studnicka et al., *Protein*

Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735; and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent

No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed
5 against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903
10 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies
15 which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For
20 example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

Polynucleotides Encoding Antibodies

The invention further provides polynucleotides comprising a nucleotide sequence
25 encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

30 The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be

assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework

regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423-42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038-1041 (1988)).

Methods of Producing Antibodies

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein.

Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not

limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell
5 systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring
10 recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant
15 antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected
20 depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al.,
25 *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase
30 (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or

factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells.

5 The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized.

10 In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & 15 Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can 20 be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion 25 desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, 30 eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS,

MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgp^rt- or ap^rt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215; and hyg^r, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.),

Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by
5 reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing
10 antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the
15 first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to
20 avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method
25 known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide
30 sequences described herein or otherwise known in the art, to facilitate purification.

The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or

portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341(1992) (said references incorporated by reference in their entireties).

As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using

methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., *Nature* 331:84-86 (1988)). The polypeptides of the present invention fused or conjugated to an antibody having disulfide-linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995)).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA; 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent

materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{111}In or ^{99}Tc .

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical

chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- α , TNF- β , AIM I (See, 5 International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, 10 lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not 15 limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 20 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of 25 Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an 30 antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

5 *Immunophenotyping*

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types.

10 Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. 15 Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic 20 stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

The antibodies of the invention may be assayed for immunospecific binding by any 25 method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, 30 immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York,

which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%-20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., ³²P or ¹²⁵I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

25 *Therapeutic Uses*

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of

the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities

include those with a dissociation constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

5

Gene Therapy

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989).

In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the

host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method

known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes
5 into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-644 (1993); Cline, *Pharmac. Ther.* 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is
10 expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

15 Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic
20 stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible
25 by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, *Cell* 71:973-985 (1992); Rheinwald, *Meth. Cell Bio.*
30 21A:229 (1980); and Pittelkow and Scott, *Mayo Clinic Proc.* 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that

expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription. Demonstration of Therapeutic or Prophylactic Activity

The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

15 *Therapeutic/Prophylactic Administration and Composition*

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral

routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); Howard et al.,

J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

5 Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector
10 and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868
15 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means
20 approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic
25 origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate,
30 glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form

of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend

on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

5 For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life
10 foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more
15 containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

20

Diagnosis and Imaging

Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity
25 of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide
30 gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the

amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule

is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

5 The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present
10 invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes
15 the first antibody may be conjugated to a detectable substrate).

 In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated
20 polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically
25 synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

 In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of
30 the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The breast/ovarian cancer antigen polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X, or the complement thereto. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 3 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

The polynucleotides of the present invention would likewise be useful for radiation
5 hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000);
10 and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular
15 disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

20 Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all
25 affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

30 Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the

invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention provides a method of detecting increased or decreased expression levels of the breast, ovarian, breast cancer and/or ovarian cancer polynucleotides in affected individuals as compared to unaffected individuals using polynucleotides of the present invention and techniques known in the art, including but not limited to the method described in Example 11. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including breast cancer and/or ovarian cancer, involving measuring the expression level of breast/ovarian cancer antigen polynucleotides in breast and/or ovarian tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard breast, ovarian, breast cancer and/or ovarian cancer polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including breast cancer and/or ovarian cancer.

In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'-mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed breast, ovarian, breast cancer and/or ovarian cancer polynucleotide expression will experience a

worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of breast, ovarian, breast cancer and/or ovarian cancer polynucleotides" is intended qualitatively or quantitatively measuring or estimating the level of the breast, ovarian, breast cancer and/or ovarian cancer polypeptide or the level of the mRNA encoding the breast, ovarian, breast cancer and/or ovarian cancer polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level in a second biological sample). Preferably, the breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the female reproductive system related disorder or being determined by averaging levels from a population of individuals not having a female reproductive system related disorder. As will be appreciated in the art, once a standard breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains breast, ovarian, breast cancer and/or ovarian cancer polypeptide or the corresponding mRNA. As indicated, biological samples include body fluids (such as vaginal pool, breast milk, lymph, sera, plasma, urine, semen, synovial fluid and spinal fluid) which contain the breast, ovarian, breast cancer and/or ovarian cancer polypeptide, breast and/or ovarian tissue, and other tissue sources found to express the breast, ovarian, breast cancer and/or ovarian cancer polypeptide. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with breast, ovarian, breast cancer and/or ovarian cancer polynucleotides attached may

be used to identify polymorphisms between the breast, ovarian, breast cancer and/or ovarian cancer polynucleotide sequences, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions, though most preferably in breast and/or ovarian related proliferative, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

The present invention encompasses breast, ovarian, breast cancer and/or ovarian cancer polynucleotides that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, Science 254, 1497 (1991); and M. Egholm, O. Buchardt, L. Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ($T_{sub.m}$) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., supra) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., supra)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not limited to treatment of proliferative disorders of hematopoietic

cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

In addition to the foregoing, a breast/ovarian cancer antigen polynucleotide can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. *Neurochem.* 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., *Nucleic Acids Research* 6: 3073 (1979); Cooney et al., *Science* 241: 456 (1988); and Dervan et al., *Science* 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., *Nucl. Acids Res.* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. *Neurochem.* 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed

on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

5 The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA
10 sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues,
15 e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific
20 polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular
25 tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to breast, ovarian, breast cancer and/or ovarian cancer polynucleotides prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue
30 cultures for contamination.

The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample.

Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower
5 levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, breast, ovarian, breast cancer and/or ovarian cancer tissues and/or cancerous and/or wounded tissues) or bodily fluids (e.g., vaginal pool, breast milk, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder,
10 relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in
15 the assayed gene expression level compared to the standard expression level is indicative of a disorder.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the
20 process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

25 Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J.
30 Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for
 5 detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium ($^{115\text{m}}\text{In}$, $^{113\text{m}}\text{In}$, ^{112}In , ^{111}In), and technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Ti), gallium
 10 (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying levels of polypeptide of the present invention in a biological
 15 sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be
 20 incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I , ^{112}In , $^{99\text{m}}\text{Tc}$, (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium ($^{115\text{m}}\text{In}$, $^{113\text{m}}\text{In}$, ^{112}In , ^{111}In), and technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Ti), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd),
 25 molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F , ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system
 30 used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99\text{m}}\text{Tc}$. The labeled antibody or

antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi , or other radioisotopes such as, for example, ^{103}Pd , ^{133}Xe , ^{131}I , ^{68}Ge , ^{57}Co , ^{65}Zn , ^{85}Sr , ^{32}P , ^{35}S , ^{90}Y , ^{153}Sm , ^{153}Gd , ^{169}Yb , ^{51}Cr , ^{54}Mn , ^{75}Se , ^{113}Sn , $^{90}\text{Yttrium}$, ^{117}Tin , $^{186}\text{Rhenium}$, $^{166}\text{Holmium}$, and $^{188}\text{Rhenium}$; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; 5 and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a breast, ovarian, breast cancer and/or ovarian cancer polypeptide of the present invention in cells or body fluid of an individual, or more
10 preferably, assaying the expression level of a breast, ovarian, breast cancer and/or ovarian cancer of the present invention in breast and/or ovarian cells or vaginal pool or breast milk of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With
15 respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or
20 further progression of the cancer.

Moreover, breast/ovarian cancer antigen polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or
25 cancerous diseases and conditions, preferably proliferative disorders of the breast and/or ovary, and/or cancerous disease and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the
30 activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing

inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described supra, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Gene Therapy Methods

Another aspect of the present invention is to gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldgrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996);

Santodonato, L., et al., *Gene Therapy* 4:1246-1255 (1997); and Zhang, J.-F. et al., *Cancer Gene Therapy* 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the
5 artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or
10 aqueous carrier.

In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or
15 precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs used in the gene therapy method are preferably
20 constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors
25 will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible
30 promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoA1 promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-

actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into
5 cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis,
10 ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the
15 lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example,
20 stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more
25 preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

30 The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues,

throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG),
5 dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can
10 be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat
15 Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

20 The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., *Methods of Immunology* (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by
25 depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate
30 solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to

the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+} -EDTA chelation (Papahadjopoulos et al., *Biochim. Biophys. Acta* (1975) 394:483; Wilson et al., *Cell* (1979) 17:77); ether injection (Deamer, D. and Bangham, A., *Biochim. Biophys. Acta* (1976) 443:629; Ostro et al., *Biochem. Biophys. Res. Commun.* (1977) 76:836; Fraley et al., Proc. Natl. Acad. Sci. USA (1979) 76:3348); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA (1979) 76:145); and reverse-phase evaporation (REV) (Fraley et al., *J. Biol. Chem.* (1980) 255:10431; Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA (1978) 75:145; Schaefer-Ridder et al., *Science* (1982) 215:166), which are
10 herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the
15 injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no.
20 WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, ex vivo or in vivo, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include,
25 but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are
30 not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, *Human Gene Therapy* 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector

may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO_4 precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

5 The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or in vivo. The transduced eukaryotic cells will express a polypeptide of the present invention.

10 In certain other embodiments, cells are engineered, ex vivo or in vivo, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have
15 been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, A. R. et al. (1974) *Am. Rev. Respir. Dis.* 109:233-238). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) *Science* 252:431-434; Rosenfeld et al., (1992) *Cell* 68:143-155). Furthermore, extensive
20 studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) *Proc. Natl. Acad. Sci. USA* 76:6606).

 Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, *Curr. Opin. Genet. Devel.* 3:499-503 (1993); Rosenfeld et al., *Cell* 68:143-155 (1992); Engelhardt et al., *Human Genet. Ther.* 4:759-769 (1993); Yang et al.,
25 *Nature Genet.* 7:362-369 (1994); Wilson et al., *Nature* 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to
30 Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, ex vivo or in vivo, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo or in vivo. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc.

Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

Preferably, the polynucleotide encoding a polypeptide of the present invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the

cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppository solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such

carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

15 **Biological Activities**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

Immune Activity

A polypeptide or polynucleotide, or agonists or antagonists of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides or polypeptides, or

agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells.

5 Polynucleotides or polypeptides, or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g.
10 agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

15 Moreover, polynucleotides or polypeptides, or agonists or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, or agonists or antagonists of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia,
20 factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides or polypeptides, or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

25 Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides or polypeptides, or agonists or
30 antagonists of the present invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of polynucleotides or polypeptides, or agonists or antagonists of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to modulate inflammation. For example, polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

Hyperproliferative Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may
5 inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing
10 T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by
15 Polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

20 Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's Macroglobulinemia, Gaucher's Disease,
25 histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

30 Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403

(1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral
5 (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-
10 dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time
15 of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

20 Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells.
25 The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve
30 administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal

antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a dissociation constant or K_d less than $5 \times 10^{-6}M$, $10^{-6}M$, $5 \times 10^{-7}M$, $10^{-7}M$, $5 \times 10^{-8}M$, $10^{-8}M$, $5 \times 10^{-9}M$, $10^{-9}M$, $5 \times 10^{-10}M$, $10^{-10}M$, $5 \times 10^{-11}M$, $10^{-11}M$, $5 \times 10^{-12}M$, $10^{-12}M$, $5 \times 10^{-13}M$, $10^{-13}M$, $5 \times 10^{-14}M$, $10^{-14}M$, $5 \times 10^{-15}M$, and $10^{-15}M$.

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998),

which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

5 Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1
10 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the
15 expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

20 Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top
25 Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or
30 polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodies of the invention may be associated with with

heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

10 **Cardiovascular Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat cardiovascular disorders, including peripheral artery disease, such as limb ischemia.

Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilog
y of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and
5 ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve disease include aortic valve insufficiency, aortic valve stenosis, hear
10 murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy,
15 hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial
20 infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomas, bacillary angiomas, Hippiel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis,
25 enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia
30 telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemia includes cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, are especially effective for the treatment of critical limb ischemia and coronary disease.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a

Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Anti-Angiogenesis Activity

5 The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and
10 spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye
15 disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological
20 conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

 The polynucleotides encoding a polypeptide of the present invention may be administered along with other polynucleotides encoding an angiogenic protein. Examples of
25 angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide
30 synthase.

 The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the

invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including breast, ovarian, prostate, lung, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid

arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque
5 neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar
10 or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of
15 hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental
20 fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular
25 degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalm.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalm.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating
30 neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation

of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired

potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

- 5 Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma.
- 10 Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a
- 15 therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

 Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist

20 in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

 Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such

25 that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

 Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic

30 joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated with the the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochelie minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated

with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-

chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

5 Diseases at the Cellular Level

Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon
10 cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary
15 cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression,
20 and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute
25 lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not
30 limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's

tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity

wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and
5 antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to
10 stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepidermic grafts, avascular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness
15 graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omentopial graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

20 It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles; hepatocytes,
25 type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present
30 invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on

the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associated with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of alveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or

polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetrachloride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Neurological Diseases

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as

cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis, cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache, migraine, dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, Hallervorden-Spatz Syndrome, hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous

system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, cerebral malaria, meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis. Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie) cerebral toxoplasmosis, central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sclerolysis which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolysaccharidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as

holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta, hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary
5 optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing
10 loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering,
15 voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus,
20 Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color
25 vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as
30 spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex

Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, Diabetic neuropathies such as diabetic foot, nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculitis such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Infectious Disease

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia

(e.g., *Borrelia burgdorferi*, Brucellosis, Candidiasis, *Campylobacter*, *Coccidioidomycosis*, Cryptococcosis, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacteriaceae (*Klebsiella*, *Salmonella* (e.g., *Salmonella typhi*, and *Salmonella paratyphi*), *Serratia*, *Yersinia*), *Erysipelothrix*, *Helicobacter*,
 5 Legionellosis, Leptospirosis, *Listeria*, Mycoplasmatales, *Mycobacterium leprae*, *Vibrio cholerae*, Neisseriaceae (e.g., *Acinetobacter*, Gonorrhea, Meningococcal), *Meisseria meningitidis*, Pasteurellacea Infections (e.g., *Actinobacillus*, *Heamophilus* (e.g., *Heamophilus influenza type B*), *Pasteurella*), *Pseudomonas*, Rickettsiaceae, Chlamydiaceae, Syphilis, *Shigella* spp., Staphylococcal, Meningiococcal, Pneumococcal and Streptococcal (e.g.,
 10 *Streptococcus pneumoniae* and Group B Streptococcus). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme
 15 Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis (e.g., meningitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections.
 20 Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, Polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, Diphtheria, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated or
 25 detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and *Trichomonas* and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparum*,
 30 *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic

infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Chemotaxis

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules
5 include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide
10 binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the
15 expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled
20 competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound
25 with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the
30 polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand

panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a
5 cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

10 Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be
15 photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide
20 probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S.
25 Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and
30 corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding

polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and $^3\text{[H]}$ thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of $^3\text{[H]}$ thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of $^3\text{[H]}$ thymidine. Both agonist and antagonist compounds may be identified by this procedure.

In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the

present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method

for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

5 In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector
10 systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an
15 inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be
20 used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

25 Drug Screening

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of
30 having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the

polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells
5 which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other
10 agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is
15 separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and
20 is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known
25 in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention
30 specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Antisense And Ribozyme (Antagonists)

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained in the cDNA contained in the related cDNA clone identified in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl₂, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the

production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature* 29:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell* 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.* 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster, et al., *Nature* 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most

efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, *Nature* 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556; Lemaitre et al., 1987, *Proc. Natl. Acad. Sci.* 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, *BioTechniques* 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine,

2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at

site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'.

5 The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the
10 intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding
15 DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

20 Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and
25 prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

30 The antagonist/agonist may also be employed to treat the diseases described herein.

Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with

overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

5 **Other Activities**

A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The
10 polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells
15 and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's
20 disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be
25 also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and
30 differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, circadian rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least
5 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the
10 deposit.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

15 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a
20 sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and
25 determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected
30 from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a

nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X; or the cDNA in the related cDNA clone identified in Table 1 which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence of the cDNA in the related cDNA clone contained in the deposit.

Also preferred is the above method for diagnosing a pathological condition which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the

group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

5 Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000 or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous
10 nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the cDNA clone referenced in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least
15 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid
20 sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a
25 polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

30 Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded by the cDNA clone referenced in Table 1; a polypeptide encoded by SEQ ID NO:X; and/or the polypeptide sequence of SEQ ID NO:Y.

5 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid
10 sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide
15 comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is a method for detecting in a biological sample a polypeptide
20 comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule
25 in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from
30 said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in

a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of:

polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

*Examples**Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample*

5 Each deposited cDNA clone is contained in a plasmid vector. Table 5 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The following correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a
 10 particular clone is identified in Table 5 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
15	Zap Express	pBK
	lalfmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
20	pCR [®] 2.1	pCR [®] 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 25 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3
 30

primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lacmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 5, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited by reference to Table 2 and 5 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone referenced in Table 1.

TABLE 5

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HUKA HUKB HUKC HUKD HUKF HUKG	Human Uterine Cancer	Lambda ZAP II	LP01
HCNA HCNB	Human Colon	Lambda Zap II	LP01
HFFA	Human Fetal Brain, random primed	Lambda Zap II	LP01
HTWA	Resting T-Cell	Lambda ZAP II	LP01
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP01
HLMB HLMF HLMG HLMH HLMI HLMJ HLMM HLMN	breast lymph node CDNA library	Lambda ZAP II	LP01
HCQA HCQB	human colon cancer	Lambda ZAP II	LP01
HMEA HMEC HMED HMEE HMEF HMEG HMEI HMEJ HMEK HMEI	Human Microvascular Endothelial Cells, fract. A	Lambda ZAP II	LP01
HUSA HUSC	Human Umbilical Vein Endothelial Cells, fract. A	Lambda ZAP II	LP01
HLQA HLQB	Hepatocellular Tumor	Lambda ZAP II	LP01
HHGA HHGB HHGC HHGD	Hemangiopericytoma	Lambda ZAP II	LP01
HSDM	Human Striatum Depression, re-rescue	Lambda ZAP II	LP01
HUSH	H Umbilical Vein Endothelial Cells, frac A, re-excision	Lambda ZAP II	LP01
HSGS	Salivary gland, subtracted	Lambda ZAP II	LP01
HFXA HFXB HFXC HFXD HFXE HFXF HFXG HFXH	Brain frontal cortex	Lambda ZAP II	LP01
HPQA HPQB HPQC	PERM TF274	Lambda ZAP II	LP01
HFXJ HFXK	Brain Frontal Cortex, re-excision	Lambda ZAP II	LP01
HCWA HCWB HCWC HCWD HCWE HCWF HCWG HCWH HCWI HCWJ HCWK	CD34 positive cells (Cord Blood)	ZAP Express	LP02
HCUA HCUB HCUC	CD34 depleted Buffy Coat (Cord Blood)	ZAP Express	LP02
HRSM	A-14 cell line	ZAP Express	LP02
HRSA	A1-CELL LINE	ZAP Express	LP02
HCUD HCUE HCUF HCUG HCUH HCUI	CD34 depleted Buffy Coat (Cord Blood), re-excision	ZAP Express	LP02
HBXE HBXF HBXG	H. Whole Brain #2, re-excision	ZAP Express	LP02
HRLM	L8 cell line	ZAP Express	LP02
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP02
HUDA HUDB HUDC	Testes	ZAP Express	LP02
HHTM HHTN HHTO	H. hypothalamus, frac A;re-excision	ZAP Express	LP02
HHTL	H. hypothalamus, frac A	ZAP Express	LP02
HASA HASD	Human Adult Spleen	Uni-ZAP XR	LP03
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP03
HE8A HE8B HE8C HE8D HE8E HE8F HE8M HE8N	Human 8 Week Whole Embryo	Uni-ZAP XR	LP03
HGBA HGBD HGBE HGBF HGBG HGBH HGBI	Human Gall Bladder	Uni-ZAP XR	LP03
HLHA HLHB HLHC HLHD HLHE HLHF HLHG HLHH HLHQ	Human Fetal Lung III	Uni-ZAP XR	LP03
HPMA HPMB HPMC HPMD HPME HPMF HPMG HPMH	Human Placenta	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP03
HSIA HSIC HSID HSIE	Human Adult Small Intestine	Uni-ZAP XR	LP03
HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEI HTEJ HTEK	Human Testes	Uni-ZAP XR	LP03
HTPA HTPB HTPC HTPD HTPE	Human Pancreas Tumor	Uni-ZAP XR	LP03
HTTA HTTB HTTC HTTD HTTE HTTF	Human Testes Tumor	Uni-ZAP XR	LP03
HAPA HAPB HAPC HAPM	Human Adult Pulmonary	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETE HETF HETG HETH HETI	Human Endometrial Tumor	Uni-ZAP XR	LP03
HHFB HHFC HHFD HHFE HHFF HHFG HHFH HHFI	Human Fetal Heart	Uni-ZAP XR	LP03
HHPB HHPC HHPD HHPE HHPF HHPG HHPH	Human Hippocampus	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCE5 HCEB HCEC HCED HCEE HCEF HCEG	Human Cerebellum	Uni-ZAP XR	LP03
HUVB HUV C HUVD HUVE	Human Umbilical Vein, Endo. remake	Uni-ZAP XR	LP03
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP03
HTAA HTAB HTAC HTAD HTAE	Human Activated T-Cells	Uni-ZAP XR	LP03
HFEA HFEB HFEC	Human Fetal Epithelium (Skin)	Uni-ZAP XR	LP03
HJPA HJPB HJPC HJPD	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Uni-ZAP XR	LP03
HESA	Human epithelioid sarcoma	Uni-Zap XR	LP03
HLTA HLTB HLTC HLTD HLTE HLTF	Human T-Cell Lymphoma	Uni-ZAP XR	LP03
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP03
HRDA HRDB HRDC HRDD HRDE HRDF	Human Rhabdomyosarcoma	Uni-ZAP XR	LP03
HCAA HCAB HCAC	Cem cells cyclohexamide treated	Uni-ZAP XR	LP03
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HSUA HSUB HSUC HSUM	Supt Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HT4A HT4C HT4D	Activated T-Cells, 12 hrs.	Uni-ZAP XR	LP03
HE9A HE9B HE9C HE9D HE9E HE9F HE9G HE9H HE9M HE9N	Nine Week Old Early Stage Human	Uni-ZAP XR	LP03
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP03
HT5A	Activated T-Cells, 24 hrs.	Uni-ZAP XR	LP03
HFGA HFGM	Human Fetal Brain	Uni-ZAP XR	LP03
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP03
HBGB HBGD	Human Primary Breast Cancer	Uni-ZAP XR	LP03
HBNA HBNB	Human Normal Breast	Uni-ZAP XR	LP03
HCAS	Cem Cells, cyclohexamide treated, subtra	Uni-ZAP XR	LP03
HHPS	Human Hippocampus, subtracted	pBS	LP03
HKCS HKCU	Human Colon Cancer, subtracted	pBS	LP03
HRGS	Raji cells, cyclohexamide treated, subtracted	pBS	LP03
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBS	LP03
HT4S	Activated T-Cells, 12 hrs, subtracted	Uni-ZAP XR	LP03
HCDA HCDB HCDC HCDD HCDE	Human Chondrosarcoma	Uni-ZAP XR	LP03
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP03
HTLA HTLB HTLC HTLD HTLE	Human adult testis, large inserts	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTLF			
HLMA HLMC HLMD	Breast Lymph node cDNA library	Uni-ZAP XR	LP03
H6EA H6EB H6EC	HL-60, PMA 4H	Uni-ZAP XR	LP03
HTXA HTXB HTXC HTXD HTXE HTXF HTXG HTXH	Activated T-Cell (12hs)/Thiouridine labelledEco	Uni-ZAP XR	LP03
HNFA HNFH HNFC HNFD HNFE HNFF HNFG HNFH HNFJ	Human Neutrophil, Activated	Uni-ZAP XR	LP03
HTOB HTOC	HUMAN TONSILS, FRACTION 2	Uni-ZAP XR	LP03
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP03
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP03
HORB	Human OB HOS treated (10 nM E2) fraction I	Uni-ZAP XR	LP03
HSVA HSVB HSVC	Human Chronic Synovitis	Uni-ZAP XR	LP03
HROA	HUMAN STOMACH	Uni-ZAP XR	LP03
HBJA HBJB HBJC HBJD HBJE HBJF HBJG HBJH HBJI HBJJ HBJK	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP03
HCRA HCRB HCRC	human corpus colosum	Uni-ZAP XR	LP03
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP03
HDSA	Dermatofibrosarcoma Protuberance	Uni-ZAP XR	LP03
HMWA HMWB HMWC HMWD HMWE HMWF HMWG HMWH HMWI HMWJ	Bone Marrow Cell Line (RS4;11)	Uni-ZAP XR	LP03
HSOA	stomach cancer (human)	Uni-ZAP XR	LP03
HERA	SKIN	Uni-ZAP XR	LP03
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP03
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP03
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP03
HBCA HBCB	H. Lymph node breast Cancer	Uni-ZAP XR	LP03
HPWT	Human Prostate BPH, re-excision	Uni-ZAP XR	LP03
HFVG HFVH HFVI	Fetal Liver, subtraction II	pBS	LP03
HNFI	Human Neutrophils, Activated, re- excision	pBS	LP03
HBMB HBMC HBMD	Human Bone Marrow, re-excision	pBS	LP03
HKML HKMM HKMN	H. Kidney Medulla, re-excision	pBS	LP03
HKIX HKIY	H. Kidney Cortex, subtracted	pBS	LP03
HADT	H. Amygdala Depression, subtracted	pBS	LP03
H6AS	HL-60, untreated, subtracted	Uni-ZAP XR	LP03
H6ES	HL-60, PMA 4H, subtracted	Uni-ZAP XR	LP03
H6BS	HL-60, RA 4h, Subtracted	Uni-ZAP XR	LP03
H6CS	HL-60, PMA 1d, subtracted	Uni-ZAP XR	LP03
HTXJ HTXK	Activated T-cell(12h)/Thiouridine-re- excision	Uni-ZAP XR	LP03
HMSA HMSB HMSC HMSE HMSE HMSF HMSG HMSH HMSI HMSJ HMSK	Monocyte activated	Uni-ZAP XR	LP03
HAGA HAGB HAGC HAGD HAGE HAGF	Human Amygdala	Uni-ZAP XR	LP03
HSRA HSRB HSRE	STROMAL -OSTEOCLASTOMA	Uni-ZAP XR	LP03
HSRD HSRF HSRG HSRH	Human Osteoclastoma Stromal Cells - unamplified	Uni-ZAP XR	LP03
HSQA HSQB HSQC HSQD HSQE	Stromal cell TF274	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HSQF HSQG			
HSKA HSKB HSKC HSKD HSKF HSKF HSKZ	Smooth muscle, serum treated	Uni-ZAP XR	LP03
HSLA HSLB HSLC HSLD HSLF HSLG	Smooth muscle, control	Uni-ZAP XR	LP03
HSDA HSDD HSDE HSDF HSDG HSDH	Spinal cord	Uni-ZAP XR	LP03
HPWS	Prostate-BPH subtracted II	pBS	LP03
HSKW HSKX HSKY	Smooth Muscle- HASTE normalized	pBS	LP03
HFPB HFPC HFPD	H. Frontal cortex, epileptic; re-excision	Uni-ZAP XR	LP03
HSDI HSDJ HSDK	Spinal Cord, re-excision	Uni-ZAP XR	LP03
HSKN HSKO	Smooth Muscle Serum Treated, Norm	pBS	LP03
HSKG HSKH HSKI	Smooth muscle, serum induced, re-exc	pBS	LP03
HFCA HFCB HFCC HFCD HFCE HFCE HFCE	Human Fetal Brain	Uni-ZAP XR	LP04
HPTA HPTB HPTD	Human Pituitary	Uni-ZAP XR	LP04
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP04
HE6B HE6C HE6D HE6E HE6F HE6G HE6S	Human Whole Six Week Old Embryo	Uni-ZAP XR	LP04
HSSA HSSB HSSC HSSD HSSE HSSF HSSG HSSH HSSI HSSJ HSSK	Human Synovial Sarcoma	Uni-ZAP XR	LP04
HE7T	7 Week Old Early Stage Human, subtracted	Uni-ZAP XR	LP04
HEPA HEPB HEPC	Human Epididymus	Uni-ZAP XR	LP04
HSNA HSNB HSNB HSNM HSNM HSNM	Human Synovium	Uni-ZAP XR	LP04
HPFB HPFC HPFD HPFE	Human Prostate Cancer, Stage C fraction	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2M HE2N HE2O	12 Week Old Early Stage Human	Uni-ZAP XR	LP04
HE2B HE2C HE2F HE2G HE2P HE2Q	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP04
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP04
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP04
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP04
HWTB HWTB HWTB	wilm's tumor	Uni-ZAP XR	LP04
HBSD	Bone Cancer, re-excision	Uni-ZAP XR	LP04
HSGB	Salivary gland, re-excision	Uni-ZAP XR	LP04
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP04
HSXA HSXB HSXC HSXD	Human Substantia Nigra	Uni-ZAP XR	LP04
HSJA HSJB HSJC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP04
HOUA HOUB HOUC HOUD HOUE	Adipocytes	Uni-ZAP XR	LP04
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP04
HELA HELB HELC HELD HELE HELF HELG HELH	Endothelial cells-control	Uni-ZAP XR	LP04
HEMA HEMB HEMC HEMD HEME HEMF HEMG HEMH	Endothelial-induced	Uni-ZAP XR	LP04
HBIA HBIB HBIC	Human Brain, Striatum	Uni-ZAP XR	LP04
HHSA HHSB HHSC HHSD HHSE	Human Hypothalamus, Schizophrenia	Uni-ZAP XR	LP04
HNGA HNGB HNGC HNGD HNGE HNGF HNGG HNGH HNGI HNGJ	neutrophils control	Uni-ZAP XR	LP04
HNHA HNHB HNHC HNHD HNHE HNHF HNHG HNHH HNHI HNHI	Neutrophils IL-1 and LPS induced	Uni-ZAP XR	LP04
HSDB HSDB	STRIATUM DEPRESSION	Uni-ZAP XR	LP04

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HHPT	Hypothalamus	Uni-ZAP XR	LP04
HSAT HSAU HSAV HSAW HSAX HSAY HSAZ	Anergic T-cell	Uni-ZAP XR	LP04
HBMS HBMT HBMU HBMV HBMW HBMX	Bone marrow	Uni-ZAP XR	LP04
HOEA HOEB HOEC HOED HOEE HOEF HOEJ	Osteoblasts	Uni-ZAP XR	LP04
HAIA HAIB HAIC HAID HAIE HAIF	Epithelial-TNF α and INF induced	Uni-ZAP XR	LP04
HTGA HTGB HTGC HTGD	Apoptotic T-cell	Uni-ZAP XR	LP04
HMCA HMCB HMCC HMCD HMCE	Macrophage-oxLDL	Uni-ZAP XR	LP04
HMAA HMAB HMAC HMAE HMAF HMAG	Macrophage (GM-CSF treated)	Uni-ZAP XR	LP04
HPHA	Normal Prostate	Uni-ZAP XR	LP04
HPIA HPIB HPIC	LNCAP prostate cell line	Uni-ZAP XR	LP04
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP04
HOSE HOSF HOSG	Human Osteoclastoma, re-excision	Uni-ZAP XR	LP04
HTGE HTGF	Apoptotic T-cell, re-excision	Uni-ZAP XR	LP04
HMAJ HMAK	H Macrophage (GM-CSF treated), re-excision	Uni-ZAP XR	LP04
HACB HACC HACD	Human Adipose Tissue, re-excision	Uni-ZAP XR	LP04
HFPA	H. Frontal Cortex, Epileptic	Uni-ZAP XR	LP04
HFAA HFAB HFAC HFAD HFAE	Alzheimers, spongy change	Uni-ZAP XR	LP04
HFAM	Frontal Lobe, Dementia	Uni-ZAP XR	LP04
HMIA HMIB HMIC	Human Manic Depression Tissue	Uni-ZAP XR	LP04
HTSA HTSE HTSF HTSG HTSH	Human Thymus	pBS	LP05
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBS	LP05
HSAA HSAB HSAC	HSA 172 Cells	pBS	LP05
HSBA HSBB HSBC HSBM	HSC172 cells	pBS	LP05
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBS	LP05
HJBA HJBB HJBC HJBD	Jurkat T-Cell, S phase	pBS	LP05
HAFA HAFB	Aorta endothelial cells + TNF- α	pBS	LP05
HAWA HAWB HAWC	Human White Adipose	pBS	LP05
HTNA HTNB	Human Thyroid	pBS	LP05
HONA	Normal Ovary, Premenopausal	pBS	LP05
HARA HARB	Human Adult Retina	pBS	LP05
HLJA HLJB	Human Lung	pCMVSPORT 1	LP06
HOFM HOFN HOFO	H. Ovarian Tumor, II, OV5232	pCMVSPORT 2.0	LP07
HOGA HOGB HOGC	OV 10-3-95	pCMVSPORT 2.0	LP07
HCGL	CD34+cells, II	pCMVSPORT 2.0	LP07
HDLA	Hodgkin's Lymphoma I	pCMVSPORT 2.0	LP07
HDTA HDTB HDTC HDTD HDTE	Hodgkin's Lymphoma II	pCMVSPORT 2.0	LP07
HKAA HKAB HKAC HKAD HKAE HKAF HKAG HKAH	Keratinocyte	pCMVSPORT2.0	LP07
HCIM	CAPFINDER, Crohn's Disease, lib 2	pCMVSPORT 2.0	LP07
HKAL	Keratinocyte, lib 2	pCMVSPORT2.0	LP07
HKAT	Keratinocyte, lib 3	pCMVSPORT2.0	LP07
HNDA	Nasal polyps	pCMVSPORT2.0	LP07
HDRA	H. Primary Dendritic Cells, lib 3	pCMVSPORT2.0	LP07

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HOHA HOHB HOHC	Human Osteoblasts II	pCMVSPORT2.0	LP07
HLDA HLDB HLDC	Liver, Hepatoma	pCMVSPORT3.0	LP08
HLDN HLDO HLDP	Human Liver, normal	pCMVSPORT3.0	LP08
HMTA	pBMC stimulated w/ poly I/C	pCMVSPORT3.0	LP08
HNTA	NTERA2, control	pCMVSPORT3.0	LP08
HDP A HDPB HDP C HDPD HDPF HDPG HDPH HDPI HDPJ HDPK	Primary Dendritic Cells, lib 1	pCMVSPORT3.0	LP08
HDP M HDP N HDPO HDP P	Primary Dendritic cells, frac 2	pCMVSPORT3.0	LP08
HMUA HMUB HMUC	Myeloid Progenitor Cell Line	pCMVSPORT3.0	LP08
HHEA HHEB HHEC HHED	T Cell helper I	pCMVSPORT3.0	LP08
HHEM HHEN HHEO HHEP	T cell helper II	pCMVSPORT3.0	LP08
HEQA HEQB HEQC	Human endometrial stromal cells	pCMVSPORT3.0	LP08
HJMA HJMB	Human endometrial stromal cells-treated with progesterone	pCMVSPORT3.0	LP08
HSWA HSWB HSWC	Human endometrial stromal cells-treated with estradiol	pCMVSPORT3.0	LP08
HSYA HSYB HSYC	Human Thymus Stromal Cells	pCMVSPORT3.0	LP08
HLWA HLWB HLWC	Human Placenta	pCMVSPORT3.0	LP08
HRAA HRAB HRAC	Rejected Kidney, lib 4	pCMVSPORT3.0	LP08
HMTM	PCR, pBMC I/C treated	PCR II	LP09
HMJA	H. Meningioma, M6	pSport 1	LP10
HMKA HMKB HMKC HMKD HMKE	H. Meningioma, M1	pSport 1	LP10
HUSG HUSI	Human umbilical vein endothelial cells, IL-4 induced	pSport 1	LP10
HUSX HUSY	Human Umbilical Vein Endothelial Cells, uninduced	pSport 1	LP10
HOFA	Ovarian Tumor I, OV5232	pSport 1	LP10
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport 1	LP10
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport 1	LP10
HADA HADC HADD HADE HADF HADG	Human Adipose	pSport 1	LP10
HOVA HOVB HOVC	Human Ovary	pSport 1	LP10
HTWB HTWC HTWD HTWE HTWF	Resting T-Cell Library, II	pSport 1	LP10
HMMA	Spleen metastatic melanoma	pSport 1	LP10
HLYA HLYB HLYC HLYD HLYE	Spleen, Chronic lymphocytic leukemia	pSport 1	LP10
HCGA	CD34+ cell, I	pSport 1	LP10
HEOM HEON	Human Eosinophils	pSport 1	LP10
HTDA	Human Tonsil, Lib 3	pSport 1	LP10
HSPA	Salivary Gland, Lib 2	pSport 1	LP10
HCHA HCHB HCHC	Breast Cancer cell line, MDA 36	pSport 1	LP10
HCHM HCHN	Breast Cancer Cell line, angiogenic	pSport 1	LP10
HCIA	Crohn's Disease	pSport 1	LP10
HDAA HDAB HDAC	HEL cell line	pSport 1	LP10
HABA	Human Astrocyte	pSport 1	LP10
HUFA HUFB HUFC	Ulcerative Colitis	pSport 1	LP10
HNTM	NTERA2 + retinoic acid, 14 days	pSport 1	LP10
HDQA	Primary Dendritic cells, CapFinder2, frac 1	pSport 1	LP10
HDQM	Primary Dendritic Cells, CapFinder, frac	pSport 1	LP10

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	2		
HLDX	Human Liver, normal.CapFinder	pSport 1	LP10
HULA HULB HULC	Human Dermal Endothelial Cells.untreated	pSport1	LP10
HUMA	Human Dermal Endothelial cells.treated	pSport1	LP10
HCJA	Human Stromal Endometrial fibroblasts, untreated	pSport1	LP10
HCJM	Human Stromal endometrial fibroblasts, treated w/ estradiol	pSport1	LP10
HEDA	Human Stromal endometrial fibroblasts, treated with progesterone	pSport1	LP10
HFNA	Human ovary tumor cell OV350721	pSport1	LP10
HKGA HKGB HKGC HKGD	Merkel Cells	pSport1	LP10
HISA HISB HISC	Pancreas Islet Cell Tumor	pSport1	LP10
HLSA	Skin, burned	pSport1	LP10
HBZA	Prostate.BPH, Lib 2	pSport 1	LP10
HBZS	Prostate BPH,Lib 2, subtracted	pSport 1	LP10
HFIA HFIB HFIC	Synovial Fibroblasts (control)	pSport 1	LP10
HFIH HFII HFIJ	Synovial hypoxia	pSport 1	LP10
HFIT HFIU HFIV	Synovial IL-1/TNF stimulated	pSport 1	LP10
HGCA	Mesangial cell, frac 1	pSport1	LP10
HMVA HMVB HMVC	Bone Marrow Stromal Cell, untreated	pSport1	LP10
HFIX HFYI HFIZ	Synovial Fibroblasts (IL1/TNF), sub	pSport1	LP10
HFOX HFOY HFOZ	Synovial hypoxia-RSF subtracted	pSport1	LP10
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP11
HLIA HLIB HLIC	Human Liver	pCMVSPORT 1	LP012
HHBA HHBB HHBC HHBD HHBE	Human Heart	pCMVSPORT 1	LP012
HBBA HBBB	Human Brain	pCMVSPORT 1	LP012
HLJA HLJB HLJC HLJD HLJE	Human Lung	pCMVSPORT 1	LP012
HOGA HOGB HOGC	Ovarian Tumor	pCMVSPORT 2.0	LP012
HTJM	Human Tonsils, Lib 2	pCMVSPORT 2.0	LP012
HAMF HAMG	KMH2	pCMVSPORT 3.0	LP012
HAAJ HAJB HAJC	L428	pCMVSPORT 3.0	LP012
HWBA HWBB HWBC HWBD HWBE	Dendritic cells, pooled	pCMVSPORT 3.0	LP012
HWAA HWAB HWAC HWAD HWAE	Human Bone Marrow, treated	pCMVSPORT 3.0	LP012
HYAA HYAB HYAC	B Cell lymphoma	pCMVSPORT 3.0	LP012
HWHG HWHH HWHI	Healing groin wound, 6.5 hours post incision	pCMVSPORT 3.0	LP012
HWHP HWHQ HWHR	Healing groin wound; 7.5 hours post incision	pCMVSPORT 3.0	LP012
HARM	Healing groin wound - zero hr post-incision (control)	pCMVSPORT 3.0	LP012
HBIM	Olfactory epithelium; nasalcavity	pCMVSPORT 3.0	LP012
HWDA	Healing Abdomen wound; 70&90 min post incision	pCMVSPORT 3.0	LP012
HWEA	Healing Abdomen Wound;15 days post incision	pCMVSPORT 3.0	LP012
HWJA	Healing Abdomen Wound:21&29 days	pCMVSPORT 3.0	LP012
HNAL	Human Tongue, frac 2	pSport1	LP012
HMJA	H. Meningioma, M6	pSport1	LP012
HMKA HMKB HMKC HMKD HMKE	H. Meningioma, M1	pSport1	LP012

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HOFA	Ovarian Tumor I, OV5232	pSport1	LP012
HCFA HCFB HCFC HCFC	T-Cell PHA 16 hrs	pSport1	LP012
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport1	LP012
HMMA HMMB HMMC	Spleen metastatic melanoma	pSport1	LP012
HTDA	Human Tonsil, Lib 3	pSport1	LP012
HDBA	Human Fetal Thymus	pSport1	LP012
HDDA	Pericardium	pSport1	LP012
HBZA	Prostate, BPH, Lib 2	pSport1	LP012
HWCA	Larynx tumor	pSport1	LP012
HWKA	Normal lung	pSport1	LP012
HSMB	Bone marrow stroma, treated	pSport1	LP012
HBHM	Normal trachea	pSport1	LP012
HLFC	Human Larynx	pSport1	LP012
HLRB	Siebben Polyposis	pSport1	LP012
HNIA	Mammary Gland	pSport1	LP012
HNJB	Palate carcinoma	pSport1	LP012
HNKA	Palate normal	pSport1	LP012
HMZA	Pharynx carcinoma	pSport1	LP012
HABG	Cheek Carcinoma	pSport1	LP012
HMZM	Pharynx Carcinoma	pSport1	LP012
HDRM	Larynx Carcinoma	pSport1	LP012
HVAA	Pancreas normal PCA4 No	pSport1	LP012
HICA	Tongue carcinoma	pSport1	LP012
HUKA HUKB HUKC HUKD HUKF	Human Uterine Cancer	Lambda ZAP II	LP013
HFFA	Human Fetal Brain, random primed	Lambda ZAP II	LP013
HTUA	Activated T-cell labeled with 4-thioluri	Lambda ZAP II	LP013
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP013
HMEB	Human microvascular Endothelial cells, fract. B	Lambda ZAP II	LP013
HUSH	Human Umbilical Vein Endothelial cells, fract. A, re-excision	Lambda ZAP II	LP013
HLQC HLQD	Hepatocellular tumor, re-excision	Lambda ZAP II	LP013
HTWJ HTWK HTWL	Resting T-cell, re-excision	Lambda ZAP II	LP013
HF6S	Human Whole 6 week Old Embryo (II), subt	pBluescript	LP013
HHPS	Human Hippocampus, subtracted	pBluescript	LP013
HLIS	LNCAP, differential expression	pBluescript	LP013
HLHS HLHT	Early Stage Human Lung, Subtracted	pBluescript	LP013
HSUS	Supt cells, cyclohexamide treated, subtracted	pBluescript	LP013
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBluescript	LP013
HSDS	H. Striatum Depression, subtracted	pBluescript	LP013
HPTZ	Human Pituitary, Subtracted VII	pBluescript	LP013
HSDX	H. Striatum Depression, subt II	pBluescript	LP013
HSDZ	H. Striatum Depression, subt	pBluescript	LP013
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBluescript SK-	LP013
HRTA	Colorectal Tumor	pBluescript SK-	LP013
HSBA HSBB HSBC HSBM	HSC172 cells	pBluescript SK-	LP013
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBluescript SK-	LP013
HJBA HJBB HJBC HJBD	Jurkat T-cell, S1 phase	pBluescript SK-	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTNA HTNB	Human Thyroid	pBluescript SK-	LP013
HAHA HAHB	Human Adult Heart	Uni-ZAP XR	LP013
HE6A	Whole 6 week Old Embryo	Uni-ZAP XR	LP013
HFC A HFCB HFCC HFCD HFCE	Human Fetal Brain	Uni-ZAP XR	LP013
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP013
HGBA HGBD HGBE HGBF HGBG	Human Gall Bladder	Uni-ZAP XR	LP013
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP013
HTEA HTEB HTEC HTEF HTEE	Human Testes	Uni-ZAP XR	LP013
HTTA HTTB HTTC HTTD HTTE	Human Testes Tumor	Uni-ZAP XR	LP013
HYBA HYBB	Human Fetal Bone	Uni-ZAP XR	LP013
HFLA	Human Fetal Liver	Uni-ZAP XR	LP013
HHFB HHFC HHFD HHFE HHFF	Human Fetal Heart	Uni-ZAP XR	LP013
HUVB HUV C HUVD HUVE	Human Umbilical Vein, End. remake	Uni-ZAP XR	LP013
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP013
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP013
HTAA HTAB HTAC HTAD HTAE	Human Activated T-cells	Uni-ZAP XR	LP013
HFEA HFEB HFEC	Human Fetal Epithelium (skin)	Uni-ZAP XR	LP013
HJPA HJPB HJPC HJPD	Human Jurkat Membrane Bound Polysomes	Uni-ZAP XR	LP013
HESA	Human Epithelioid Sarcoma	Uni-ZAP XR	LP013
HALS	Human Adult Liver, Subtracted	Uni-ZAP XR	LP013
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP013
HCAA HCAB HCAC	Cem cells, cyclohexamide treated	Uni-ZAP XR	LP013
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP013
HE9A HE9B HE9C HE9D HE9E	Nine Week Old Early Stage Human	Uni-ZAP XR	LP013
HSFA	Human Fibrosarcoma	Uni-ZAP XR	LP013
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP013
HTRA	Human Trachea Tumor	Uni-ZAP XR	LP013
HE2A HE2D HE2E HE2H HE2I	12 Week Old Early Stage Human	Uni-ZAP XR	LP013
HE2B HE2C HE2F HE2G HE2P	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP013
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP013
HBGA	Human Primary Breast Cancer	Uni-ZAP XR	LP013
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP013
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP013
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP013
HTOA HTOD HTOE HTOF HTOG	human tonsils	Uni-ZAP XR	LP013
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP013
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP013
HOQB	Human OB HOS treated (1 nM E2) fraction I	Uni-ZAP XR	LP013
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP013
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP013
HROA HROC	HUMAN STOMACH	Uni-ZAP XR	LP013
HBJA HBJB HBJC HBJD HBJE	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP013
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP013
HCPA	Corpus Callosum	Uni-ZAP XR	LP013
HSOA	stomach cancer (human)	Uni-ZAP XR	LP013
HERA	SKIN	Uni-ZAP XR	LP013
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP013
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HWTB HWTB HWTB	wilm's tumor	Uni-ZAP XR	LP013
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP013
HAPN HAPN HAPN HAPQ HAPR	Human Adult Pulmonary;re-excision	Uni-ZAP XR	LP013
HLTG HLTH	Human T-cell lymphoma;re-excision	Uni-ZAP XR	LP013
HAHC HAHD HAHE	Human Adult Heart;re-excision	Uni-ZAP XR	LP013
HAGA HAGB HAGC HAGD HAGE	Human Amygdala	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle-IL1b induced	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP013
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP013
HPJA HPJB HPJC	LNCAP prostate cell line	Uni-ZAP XR	LP013
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP013
HBTA	Bone Marrow Stroma. TNF&LPS ind	Uni-ZAP XR	LP013
HMCF HMCG HMCH HMCJ HMCJ	Macrophage-oxLDL; re-excision	Uni-ZAP XR	LP013
HAGG HAGH HAGI	Human Amygdala;re-excision	Uni-ZAP XR	LP013
HACA	H. Adipose Tissue	Uni-ZAP XR	LP013
HKFB	K562 + PMA (36 hrs).re-excision	ZAP Express	LP013
HCWT HCWU HCWV	CD34 positive cells (cord blood),re-ex	ZAP Express	LP013
HBWA	Whole brain	ZAP Express	LP013
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP013
HAVM	Temporal cortex-Alzheimer	pT-Adv	LP014
HAVT	Hippocampus, Alzheimer Subtracted	pT-Adv	LP014
HHAS	CHME Cell Line	Uni-ZAP XR	LP014
HBJR	Larynx normal	pSport 1	LP014
HWLE HWLF HWLG HWLH	Colon Normal	pSport 1	LP014
HCRM HCRN HCRO	Colon Carcinoma	pSport 1	LP014
HWLI HWLJ HWLK	Colon Normal	pSport 1	LP014
HWLQ HWLR HWLS HWLT	Colon Tumor	pSport 1	LP014
HBFM	Gastrocnemius Muscle	pSport 1	LP014
HBOD HBOE	Quadriceps Muscle	pSport 1	LP014
HBKD HBKE	Soleus Muscle	pSport 1	LP014
HCCM	Pancreatic Langerhans	pSport 1	LP014
HWGA	Larynx carcinoma	pSport 1	LP014
HWGM HWGN	Larynx carcinoma	pSport 1	LP014
HWLA HWLB HWLC	Normal colon	pSport 1	LP014
HWLM HWLN	Colon Tumor	pSport 1	LP014
HVAM HVAN HVAO	Pancreas Tumor	pSport 1	LP014
HWGQ	Larynx carcinoma	pSport 1	LP014
HAQM HAQN	Salivary Gland	pSport 1	LP014
HASM	Stomach; normal	pSport 1	LP014
HBCM	Uterus; normal	pSport 1	LP014
HCDM	Testis; normal	pSport 1	LP014
HDJM	Brain; normal	pSport 1	LP014
HEFM	Adrenal Gland,normal	pSport 1	LP014
HBAA	Rectum normal	pSport 1	LP014
HFDM	Rectum tumour	pSport 1	LP014
HGAM	Colon, normal	pSport 1	LP014
HHMM	Colon, tumour	pSport 1	LP014
HCLB HCLC	Human Lung Cancer	Lambda Zap II	LP015
HRLA	L1 Cell line	ZAP Express	LP015

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HHAM	Hypothalamus. Alzheimer's	pCMVSPORT 3.0	LP015
HKBA	Ku 812F Basophils Line	pSport 1	LP015
HS2S	Saos2. Dexamethosone Treated	pSport 1	LP016
HA5A	Lung Carcinoma A549 TNFalpha activated	pSport 1	LP016
HTFM	TF-1 Cell Line GM-CSF Treated	pSport 1	LP016
HYAS	Thyroid Tumour	pSport 1	LP016
HUTS	Larynx Normal	pSport 1	LP016
HXOA	Larynx Tumor	pSport 1	LP016
HEAH	Ea.hy.926 cell line	pSport 1	LP016
HINA	Adenocarcinoma Human	pSport 1	LP016
HRMA	Lung Mesothelium	pSport 1	LP016
HLCL	Human Pre-Differentiated Adipocytes	Uni-Zap XR	LP017
HS2A	Saos2 Cells	pSport 1	LP020
HS2I	Saos2 Cells; Vitamin D3 Treated	pSport 1	LP020
HUCM	CHME Cell Line, untreated	pSport 1	LP020
HEPN	Aryepiglottis Normal	pSport 1	LP020
HPSN	Sinus Piniiformis Tumour	pSport 1	LP020
HNSA	Stomach Normal	pSport 1	LP020
HNSM	Stomach Tumour	pSport 1	LP020
HNLA	Liver Normal Met5No	pSport 1	LP020
HUTA	Liver Tumour Met 5 Tu	pSport 1	LP020
HOCN	Colon Normal	pSport 1	LP020
HOCT	Colon Tumor	pSport 1	LP020
HTNT	Tongue Tumour	pSport 1	LP020
HLXN	Larynx Normal	pSport 1	LP020
HLXT	Larynx Tumour	pSport 1	LP020
HTYN	Thymus	pSport 1	LP020
HPLN	Placenta	pSport 1	LP020
HTNG	Tongue Normal	pSport 1	LP020
HZAA	Thyroid Normal (SDCA2 No)	pSport 1	LP020
HWES	Thyroid Thyroiditis	pSport 1	LP020
HFHD	Ficolled Human Stromal Cells, 5Fu treated	pTriplEx2	LP021
HFHM,HFHN	Ficolled Human Stromal Cells, Untreated	pTriplEx2	LP021
HPCI	Hep G2 Cells, lambda library	lambda Zap-CMV XR	LP021
HBCA,HBCB,HBCC	H. Lymph node breast Cancer	Uni-ZAP XR	LP021
HCOK	Chondrocytes	pSPORT1	LP022
HDCA, HDCB, HDCC	Dendritic Cells From CD34 Cells	pSPORT1	LP022
HDMA, HDMB	CD40 activated monocyte dendritic cells	pSPORT1	LP022
HDDM, HDDN, HDDO	LPS activated derived dendritic cells	pSPORT1	LP022
HPCR	Hep G2 Cells, PCR library	lambda Zap-CMV XR	LP022
HAAA, HAAB, HAAC	Lung, Cancer (4005313A3): Invasive Poorly Differentiated Lung Adenocarcinoma	pSPORT1	LP022
HIPA, HIPB, HIPC	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic	pSPORT1	LP022
HOOH, HOOI	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low	pSPORT1	LP022

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	Malignant Pot		
HIDA	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HUJA.HUJB.HUJC.HUJD.HUJE	B-Cells	pCMVSPORT 3.0	LP022
HNOA.HNOB.HNOC.HNOD	Ovary, Normal: (9805C040R)	pSPORT1	LP022
HNLM	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HSCL	Stromal Cells	pSPORT1	LP022
HAAX	Lung, Cancer: (4005313 A3) Invasive Poorly-differentiated Metastatic lung adenocarcinoma	pSPORT1	LP022
HUUA.HUUB.HUUC.HUUD	B-cells (unstimulated)	pTriplEx2	LP022
HWWA.HWWB,HWWC.HWWD,HVWE.HWWF.HWWG	B-cells (stimulated)	pSPORT1	LP022
HCCC	Colon, Cancer: (9808C064R)	pCMVSPORT 3.0	LP023
HPDO HPDP HPDQ HPDR HPD	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	pSport 1	LP023
HPCO HPCP HPCQ HPCT	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	pSport 1	LP023
HOCM HOCO HOCB HOCQ	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	pSport 1	LP023
HCBM HCBN HCBO	Breast, Cancer: (4004943 A5)	pSport 1	LP023
HNBT HNBH HNBV	Breast, Normal: (4005522B2)	pSport 1	LP023
HBCP HBCQ	Breast, Cancer: (4005522 A2)	pSport 1	LP023
HBCJ	Breast, Cancer: (9806C012R)	pSport 1	LP023
HSAM HSAN	Stromal cells 3.88	pSport 1	LP023
HVCA HVCB HVCC HVCD	Ovary, Cancer: (4004332 A2)	pSport 1	LP023
HSCK HSEN HSEO	Stromal cells (HBM3.18)	pSport 1	LP023
HSCP HSCQ	stromal cell clone 2.5	pSport 1	LP023
HUXA	Breast Cancer: (4005385 A2)	pSport 1	LP023
HCOM HCON HCOO HCOP HCOQ	Ovary, Cancer (4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	pSport 1	LP023
HBNM	Breast, Cancer: (9802C020E)	pSport 1	LP023
HVVA HVVB HVVC HVVD HVVE	Human Bone Marrow, treated	pSport 1	LP023

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 5. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to the nucleotide sequence of SEQ ID NO:X.

5 Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P - γ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid
10 mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using
15 Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

 Alternatively, two primers of 17-20 nucleotides derived from both ends of the
20 nucleotide sequence of SEQ ID NO:X are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 μg of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl_2 , 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of
25 Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA
30 product.

 Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not

limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

5 Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full
10 length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the
15 RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis
20 using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

25

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the sequence corresponding to SEQ ID NO:X, according to the method
30 described in Example 1. (See also, Sambrook.)

Example 3: Tissue specific expression analysis

The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue specific cDNA libraries. Libraries generated from a particular tissue are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs which show tissue specific expression are selected.

The original clone from which the specific EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured then transferred in 96 well format to a nylon membrane (Schleicher and Schuell) generating an array filter of tissue specific clones. Housekeeping genes, maize genes, and known tissue specific genes are included on the filters. These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed. The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified and the full length sequence of these clones is generated.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute

cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR
5 fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using
10 PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial
15 expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is
20 ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is
25 isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto
30 pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid (5 "Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 (10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The (15 recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. (20 The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase (25 gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, (30 BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction

sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express
5 protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E*
10 *coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell
15 paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then
20 mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is
25 discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous
30 stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μ m membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column
5 is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of
10 water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging
15 from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from
20 Commassie blue stained 16% SDS-PAGE gel when 5 μ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

25

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of
30 recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under

control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

5 Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

10 Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard
15 methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with
20 appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

25 The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the
30 cloned fragment is confirmed by DNA sequencing.

Five μ g of a plasmid containing the polynucleotide is co-transfected with 1.0 μ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA",

Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μ g of BaculoGold™ virus DNA and 5 μ g of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μ l Lipofectin plus 90 μ l Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 μ l of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 μ Ci of 35 S-methionine and 5 μ Ci 35 S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human HeLa, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used

for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μ g of the expression plasmid pC6 or pC4 is cotransfected with 0.5 μ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10,

25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well
5 plates containing even higher concentrations of methotrexate (1 μ M, 2 μ M, 5 μ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

10 *Example 9: Protein Fusions*

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding
15 protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion
20 proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

25 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be
30 ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the

vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the polypeptide of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

10 GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCCCAG
CACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAACCCAAGGA
CACCTCATGATCTCCCGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGC
CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT
AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC
15 AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCC
AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAG
CTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGC
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGAC
20 CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACC
GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT
GAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:837)

25 *Example 10: Production of an Antibody from a Polypeptide*

a) Hybridoma Technology

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide

of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide of the present invention are prepared using hybridoma technology. (Kohler et al., *Nature* 256:495 (1975); Kohler et al., *Eur. J. Immunol.* 6:511 (1976); Kohler et al., *Eur. J. Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas*, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide of the present invention or, more preferably, with a secreted polypeptide of the present invention-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (*Gastroenterology* 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

Alternatively, additional antibodies capable of binding to polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide of the present invention-specific antibody can be blocked by polypeptide of the present invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide of the present invention-specific antibody and are used to immunize an animal to induce formation of further polypeptide of the present invention-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

b) Isolation Of Antibody Fragments Directed Against Polypeptide of the Present Invention From A Library Of scFvs

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 10⁹ E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10⁸ TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra

8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter
5 (Minisart NML; Sartorius) to give a final concentration of approximately 10¹³ transducing units/ml (ampicillin-resistant clones).

Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately
10 10¹³ TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4.
15 Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing
20 increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones
25 positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype
5 of interest (such as a disease) is be isolated. cDNA is then generated from these RNA
samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a
template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X;
and/or the nucleotide sequence of the related cDNA in the cDNA clone contained in a
deposited library. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30
10 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using
buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4
polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The
intron-exon borders of selected exons is also determined and genomic PCR products
15 analyzed to confirm the results. PCR products harboring suspected mutations is then cloned
and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic
Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States
Biochemical). Affected individuals are identified by mutations not present in unaffected
20 individuals.

Genomic rearrangements are also observed as a method of determining alterations in
a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2
are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim),
and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991).
25 Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA
for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium
iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are
obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination
30 with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable
excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image

collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 13: Formulation

The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed
5 herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant a polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good
10 medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the
15 Therapeutic administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given
20 continuously, the Therapeutic is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

25 Therapeutics can be are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of
30 administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray.

5 "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release
10 systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

15 Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., *Biopolymers* 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., *Id.*) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

20 Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. (USA)* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci.(USA)*
25 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being
30 adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987);

Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated
5 generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the
10 Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such
15 carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate,
20 succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including
25 cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be
30 understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is

readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

5 Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic
10 using bacteriostatic Water-for-Injection.

 The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products,
15 which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

 The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention
20 include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include,
25 but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping
30 cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or

concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate
5 administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories,
10 conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous
15 lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited
20 to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No. WO
25 98/30694), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7
30 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICLOVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or

prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment,

5 Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection.

10 In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an

15 opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the

20 Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases,

25 aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

Conventional nonspecific immunosuppressive agents, that may be administered in

30 combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone,

azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

In specific embodiments, Therapeutics of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucocorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine);

cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol
5 diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

In a specific embodiment, Therapeutics of the invention are administered in
10 combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

15 In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not
20 limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth
25 Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors,
30 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2

(VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Example 14: Method of Treating Decreased Levels of the Polypeptide

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide of the present invention in an individual can be treated by administering the agonist or antagonist of the present invention. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist or

antagonist to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist or antagonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

5

Example 15: Method of Treating Increased Levels of the Polypeptide

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to
10 such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

15 For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 13.

20 *Example 16: Method of Treatment Using Gene Therapy-Ex Vivo*

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces.
25 Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated
30 at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer

is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on
5 agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a
10 HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the
15 gene of interest properly inserted.

The amphotropic pA317 or GP+aml2 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce
20 infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer
25 cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his.
30 Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after

having been grown to confluence on cytodex 3 microcarrier beads.

Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention

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Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; 10 International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting 15 sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct 20 restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the 25 appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

30 In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral

particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na₂HPO₄, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately 3×10^6 cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 µg/ml. 0.5 ml of the cell suspension (containing approximately 1.5×10^6 cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 µF and 250-300 V,

respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and
5 the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having
10 been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 18: Method of Treatment Using Gene Therapy - In Vivo

15 Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary
20 for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al.,
25 Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

30 The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell,

including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will

appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 19: Transgenic Animals

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (*i.e.*, polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, *e.g.*, Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci.

USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

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Example 20: Knock-Out Animals

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding

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sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 22: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation

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Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a

positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15.

5 Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the
15 detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

In Vitro Assay- Agonists or antagonists of the invention can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the agonists or antagonists of the invention
20 on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell
25 proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to
30 which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5×10^{-5} M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well)

with ³H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of agonists or antagonists of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with agonists or antagonists of the invention identify the results of the activity of the agonists or antagonists on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with agonist or antagonist is used to indicate whether the agonists or antagonists specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and agonists or antagonists-treated mice.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 23: T Cell Proliferation Assay

A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ³H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 µl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 µg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10⁴/well) of mAb coated plates

in RPMI containing 10% FCS and P/S in the presence of varying concentrations of agonists or antagonists of the invention (total volume 200 μ l). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 μ l of supernatant is removed and stored -20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 μ l of medium containing 0.5 μ Ci of 3 H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of 3 H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of agonists or antagonists of the invention.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 24: Effect of Agonists or Antagonists of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells

Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- α , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC γ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of agonist or antagonist of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow

cytometry on a FACScan (Becton Dickinson).

Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells (10^6 /ml) are treated with increasing concentrations of agonists or antagonists of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of agonists or antagonists of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Agonists or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified

from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

- 5 Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in
10 polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of 2×10^6 /ml in PBS containing PI at a final concentration of 5 μ g/ml, and then incubated at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in
15 this experimental paradigm.

Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows.

- 20 Human monocytes are incubated at a density of 5×10^5 cells/ml with increasing concentrations of agonists or antagonists of the invention and under the same conditions, but in the absence of agonists or antagonists. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of agonist or antagonist of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use.
25 Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e. g, R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

- Oxidative burst. Purified monocytes are plated in 96-w plate at 2×10^5 cell/well. Increasing
30 concentrations of agonists or antagonists of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To

the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 µl 1N NaOH per well. The
5 absorbance is read at 610 nm. To calculate the amount of H₂O₂ produced by the macrophages, a standard curve of a H₂O₂ solution of known molarity is performed for each experiment.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test
10 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 25: Biological Effects of Agonists or Antagonists of the Invention

15 Astrocyte and Neuronal Assays.

Agonists or antagonists of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for
20 the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an agonist or antagonist of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on
25 cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not
30 necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal

culture paradigm, the ability of an agonist or antagonist of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

5 Fibroblast and endothelial cell assays.

Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate
10 for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE₂ assays,
15 the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or agonists or antagonists of the invention with or without IL-1 α for 24 hours. The supernatants are collected and assayed for PGE₂ by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one
20 day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without agonists or antagonists of the invention IL-1 α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or agonists or antagonists of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on
25 growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with agonists or antagonists of the invention.

Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of
30 striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection

neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP⁺) and released. Subsequently, MPP⁺ is actively accumulated in
5 dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP⁺ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has
10 trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

15 Based on the data with FGF-2, agonists or antagonists of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an agonist or antagonist of the invention is first examined *in vitro* in a
20 dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm² on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with
25 paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

Since the dopaminergic neurons are isolated from animals at gestation day 14, a
30 developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*.

Therefore, if an agonist or antagonist of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the agonist or antagonist may be involved in Parkinson's Disease.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 26: The Effect of Agonists or Antagonists of the Invention on the Growth of Vascular Endothelial Cells

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at 2.5×10^4 cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An agonist or antagonist of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the compound of the invention may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cell indicates that the compound of the invention inhibits vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 27: Rat Corneal Wound Healing Model

This animal model shows the effect of an agonist or antagonist of the invention on neovascularization. The experimental protocol includes:

- a) Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.
- b) Inserting a spatula below the lip of the incision facing the outer corner of the

eye.

c) Making a pocket (its base is 1-1.5 mm from the edge of the eye).

d) Positioning a pellet, containing 50ng- 5ug of an agonist or antagonist of the invention, within the pocket.

5 e) Treatment with an agonist or antagonist of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test
10 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 28: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models

A. Diabetic db+/db+ Mouse Model.

15 To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner,
20 M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal
25 recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am. J. of Pathol.* 114:46-
30 55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*,

Diabetes 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

5 The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The
10 animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

15 Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical
20 area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with
25 sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no
30 longer visible and the wound is covered by a continuous epithelium.

An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups

received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an agonist or antagonist of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue

control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

- 5 Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

B. Steroid Impaired Rat Model

- The inhibition of wound healing by steroids has been well documented in various *in vitro* and
10 *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *Am. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*,
15 *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish
20 phenomenon in rats (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

- To demonstrate that an agonist or antagonist of the invention can accelerate the
25 healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

- Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are
30 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All

manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

5 The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials
10 are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on
15 days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups
20 received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

25 Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the
30 differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm^2 , the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned
5 perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine
hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds.
Histologic examination of the wounds allows assessment of whether the healing process and
the morphologic appearance of the repaired skin is improved by treatment with an agonist or
antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to
10 determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is
considered significant.

The studies described in this example tested activity of agonists or antagonists of the
invention. However, one skilled in the art could easily modify the exemplified studies to test
15 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 29: Lymphedema Animal Model

The purpose of this experimental approach is to create an appropriate and consistent
20 lymphedema model for testing the therapeutic effects of an agonist or antagonist of the
invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in
the rat hind limb. Effectiveness is measured by swelling volume of the affected limb,
quantification of the amount of lymphatic vasculature, total blood plasma protein, and
histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly,
25 the chronic progress of the edema is followed for up to 3-4 weeks.

Prior to beginning surgery, blood sample is drawn for protein concentration analysis.
Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the
right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in
70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric
30 measurements are made prior to injecting dye into paws after marking 2 measurement levels
(0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left
paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric

measurements are then made following injection of dye into paws.

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel
5 that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosus and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and
10 ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of
15 ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the
20 intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

25 Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with
30 Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped

into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca²⁺ comparison.

5 Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

10 Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test
15 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 30: Suppression of TNF alpha-induced adhesion molecule expression by a Agonist or Antagonist of the Invention

20 The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial
25 leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

30 Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of an agonist or antagonist of the invention to mediate a suppression of TNF- α induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF- α treated ECs when co-stimulated with a member of the FGF family of proteins.

5 To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO₂. HUVECs are seeded in 96-well plates at concentrations of 1×10^4 cells/well in EGM medium at 37 degree C for 18-24 hrs or
10 until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well
15 plate to confluence. Growth medium is removed from the cells and replaced with 90 μ l of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μ l volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μ l of 0.1% paraformaldehyde-PBS(with Ca⁺⁺ and Mg⁺⁺) is added
20 to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 μ l of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μ g/ml (1:10 dilution of 0.1
25 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20 μ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH
30 10.4). 100 μ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: $1:5,000 (10^0) > 10^{-0.5} > 10^{-1} > 10^{-1.5}$. 5 μ l of each dilution is added to triplicate

wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μ l of pNPN reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 μ l of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on
5 blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test
10 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 31: Production Of Polypeptide of the Invention For High-Throughput Screening Assays

15 The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 33-42.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working
20 solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for
25 up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2×10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

30 The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing

a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add
5 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then
10 person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with
15 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl₂ (anhyd); 0.00130 mg/L CuSO₄-5H₂O; 0.050 mg/L of Fe(NO₃)₃-9H₂O; 0.417 mg/L of FeSO₄-7H₂O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl₂; 48.84 mg/L of MgSO₄; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO₃; 62.50 mg/L of NaH₂PO₄-H₂O; 71.02 mg/L of Na₂HPO₄; .4320 mg/L of ZnSO₄-7H₂O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-
20 Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L- Arginine-HCL; 7.50 mg/ml of L-Asparagine-H₂O; 6.65 mg/ml of L-Aspartic Acid; 29.56
25 mg/ml of L-Cystine-2HCL-H₂O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L- Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L- Histidine-HCL-H₂O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22
30 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H₂O; and 99.65 mg/ml of L-

Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B₁₂; 25 mM of
5 HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust
10 osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml
15 appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 33-40.

20 It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant
25 characterized by an activity in a particular assay.

Example 32: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and proliferation of
30 cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements

alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:838)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

381

	<u>Ligand</u>	<u>JAKs</u>				<u>STATS GAS(elements) or ISRE</u>	
		<u>tyk2</u>	<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>		
	<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
	IL-10	+	?	?	-	1,3	
	<u>gp130 family</u>						
10	IL-6 (Pleiotrohic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
	IL-11(Pleiotrohic)	?	+	?	?	1,3	
	OnM(Pleiotrohic)	?	+	+	?	1,3	
	LIF(Pleiotrohic)	?	+	+	?	1,3	
	CNTF(Pleiotrohic)	-/+	+	+	?	1,3	
15	G-CSF(Pleiotrohic)	?	+	?	?	1,3	
	IL-12(Pleiotrohic)	+	-	+	+	1,3	
	<u>g-C family</u>						
	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
20	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP
	>>Ly6)(IgH)						
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
25	IL-15	?	+	?	+	5	GAS
	<u>gp140 family</u>						
	IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5	GAS
30	GM-CSF (myeloid)	-	-	+	-	5	GAS
	<u>Growth hormone family</u>						
	GH	?	-	+	-	5	
	PRL	?	+/-	+	-	1,3,5	
35	EPO	?	-	+	-	5	GAS(B-

382

CAS>IRF1=IFP>>Ly6)

Receptor Tyrosine Kinases

	EGF	?	+	+	-	1,3	GAS (IRF1)
5	PDGF	?	+	+	-	1,3	
	CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 33-34, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

10 5':GCGCCTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATGATTTCCTCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:839)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTGGCAAAGCCTAGGC:3' (SEQ ID NO:840)

15 PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

20 5':CTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATGATTTCCTCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCGCCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTA
25 GGCTTTTGGAAAAAGCTT:3' (SEQ ID NO:841)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

30

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 33-34.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 35 and 36. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 33: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the

GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC
5 Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately
10 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells
15 containing 200 ul of cells. Thus, it is either scaled up; or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

20 During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1×10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

25 The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptide of the present invention or polypeptide of the present invention induced polypeptides as produced by the protocol described in Example 31.

30 On the day of treatment with the supernatant, the cells should be washed and

resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

5 Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

 After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12
10 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

 The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul
15 samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 37. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

20 As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

 The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

25

Example 34: High-Throughput Screening Assay Identifying Myeloid Activity

 The following protocol is used to assess myeloid activity of polypeptide of the present invention by determining whether polypeptide of the present invention
30 proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using

the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

5 To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 32, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2×10^7 U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml
10 penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, 1 mM MgCl_2 , and 675 uM CaCl_2 . Incubate at 37 degrees C for 45 min.

15 Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

20 These cells are tested by harvesting 1×10^8 cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of 5×10^5 cells/ml. Plate 200 ul cells per well in the 96-well plate (or 1×10^5 cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example
25 31. Incubate at 37 degree C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 37.

30 *Example 35: High-Throughput Screening Assay Identifying Neuronal Activity.*

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by polypeptide of the present invention.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat pheochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by polypeptide of the present invention can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:842)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:843)

Using the GAS:SEAP/Neo vector produced in Example 32, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and

allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 31. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as 5×10^5 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 ul supernatant produced by Example 31, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 37.

Example 36: High-Throughput Screening Assay for T-cell Activity

NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide

variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class I MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 31. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:844), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTCCGGGGACTTTCCGGGAC
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:845)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:840)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)

Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC
5 ATCCCGCCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCGATGGCTGA
CTAATTTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTA
TTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA
GCTT:3' (SEQ ID NO:846)

Next, replace the SV40 minimal promoter element present in the pSEAP2-
10 promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and
HindIII. However, this vector does not contain a neomycin resistance gene, and
therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP
cassette is removed from the above NF-KB/SEAP vector using restriction enzymes
15 SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly,
the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the
GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are
created and maintained according to the protocol described in Example 33. Similarly,
20 the method for assaying supernatants with these stable Jurkat T-cells is also described
in Example 33. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to
wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 37: Assay for SEAP Activity

25

As a reporter molecule for the assays described in Examples 33-36, SEAP
activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the
following general procedure. The Tropix Phospho-light Kit supplies the Dilution,
Assay, and Reaction Buffers used below.

30

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x

dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

- 5 Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at
- 10 each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

15

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25

393

24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 38: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants
5 which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to
10 measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star
15 black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate
20 is incubated at 37 degrees C in a CO₂ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to $2-5 \times 10^6$ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension.
25 The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1×10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

30 For a non-cell based assay, each well contains a fluorescent molecule, such as

fluo-4 . The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular Ca^{++} concentration.

10

Example 40: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

20 Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

25 Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol

30

is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 31, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na₃VO₄, 2 mM Na₄P₂O₇ and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4

degree C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

5 Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for
10 a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg₂⁺ (5mM ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂,
15 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initiate the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

20 Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-
25 POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound
30 peroxidase activity is quantitated using an ELISA reader and reflects the level of

tyrosine kinase activity.

Example 41: High-Throughput Screening Assay Identifying Phosphorylation Activity

5 As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 40, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other
10 molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

 Specifically, assay plates are made by coating the wells of a 96-well ELISA
15 plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody
20 detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

 A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants
25 obtained in Example 31 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

 After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit)
30 antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the

Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased
5 fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

Example 42: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation

10 This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond.
15 Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in
20 such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or
25 agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells
30 are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-

glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5×10^5 cells/ml. During this time, 100 μ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that
5 can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 μ l of prepared cytokines, 50 μ l of the supernatants prepared in Example 31 (supernatants at 1:2 dilution = 50 μ l) and 20 μ l of diluted cells are added to the media
10 which is already present in the wells to allow for a final total volume of 100 μ l. The plates are then placed in a 37°C/5% CO₂ incubator for five days.

Eighteen hours before the assay is harvested, 0.5 μ Ci/well of [3H] Thymidine is added in a 10 μ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat
15 using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 μ l Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined
20 via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene
25 therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell
30 proliferation and/or to decrease the inhibition of cell proliferation in the presence of

cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

Example 43: Assay for Extracellular Matrix Enhanced Cell Response (EMECR)

10 The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

15 Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5\beta_1$ and $\alpha_4\beta_1$ integrin
20 receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

25 Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of $0.2 \mu\text{g}/\text{cm}^2$. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem

cells is to be expected. Gene products of the invention (e.g., including, but not limited to, polynucleotides and polypeptides of the present invention, and supernatants produced in Example 31), are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO₂, 7% O₂, and 88% N₂) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

If a particular polypeptide of the present invention is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene encoding said polypeptide may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of

interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

Example 44: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation

10 The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or
15 smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without
20 co-TNF α stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 μ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 μ g/ml
25 hEGF, 5mg/ml insulin, 1 μ g/ml hFGF, 50mg/ml gentamycin, 50 μ g/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours, culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50 μ g/ml Amphotericin B,
30 0.4% FBS. Incubate at 37°C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNF α is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or polypeptides
5 of the present invention and incubate at 37°C/5% CO₂ until day 5.

Transfer 60 μ l from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4°C until Day 6 (for IL6 ELISA). To the remaining 100 μ l in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the
10 culture volume (10 μ l). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 μ l/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON
15 at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 μ l/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 μ l/well of
20 diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker. Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 μ l/well. Cover the plate and incubate 1 h at RT.
25 Plates are again washed with wash buffer and blotted on paper towels. Add 100 μ l/well of Enhancement Solution and shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay are tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the
30 polypeptide of the present invention may be involved in dermal fibroblast

proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the polynucleotide/polypeptide of the present invention which gives a positive result. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the present invention and polynucleotides of the present invention may be used in wound healing and dermal regeneration, as well as the promotion of vasculargenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides and polynucleotides of the invention may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides and polynucleotides of the invention may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 45: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells

5 The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1
10 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor
15 participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 μ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the
20 plate in triplicate (in 10 μ l volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μ l of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA
25 and drained. 10 μ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 μ l of diluted ExtrAvidin-Alkaline
30 Phosphotase (1:5,000 dilution, referred to herein as the working dilution) are added to

each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNPP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

15 *Example 46: Alamar Blue Endothelial Cells Proliferation Assay*

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with

GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days.

- 5 After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

- Alamar blue is an oxidation-reduction indicator that both fluoresces and
10 changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and
15 inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

20

Example 47: Detection of Inhibition of a Mixed Lymphocyte Reaction

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides).

- 25 Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and

natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM[®], density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2×10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2×10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 μ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO₂, and 1 μ C of [³H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

- 5 The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both
- 10 incorporated herein by reference in their entireties. Moreover, the hard copy of and the corresponding computer readable form of the Sequence Listing of Serial No. 60/124,270 are also incorporated herein by reference in their entireties.

Applicant's or agent's file reference number	PA103PCT	International application no.
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209059</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
RO/US 08 MAR 2000	
Authorized officer <u>Torilisa Harrod</u>	Authorized officer
<u>PCT/Internat'l Appl Processing Div.</u>	
<u>(703) 305-3670</u>	

ATCC Deposit No. 209059**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209059

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

414

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209060</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application RO/US 08 MAR 2000 Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. (703) 305-3670	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
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ATCC Deposit No. 209060**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209060

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

417

Applicant's or agent's file reference number	PA103PCT	International application N
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209061</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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ATCC Deposit No. 209061**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209061

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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420

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209062
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
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Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. (703) 305-3570	Authorized officer

ATCC Deposit No. 209062**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209062

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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423

Applicant's or agent's file reference number	PA103PCT	International application i
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209063</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application RO/US 20 MAR 2000 Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. (703) 305-9670	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
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ATCC Deposit No. 209063**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2

ATCC Deposit No. 209063

DENMARK

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SWEDEN

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426

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209064</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
RO/US 09 MAR 2000	
Authorized officer <u>Yolanda Harrod</u> <u>PCT/Internat'l Appl Processing Div.</u> <u>(703) 305-3670</u>	Authorized officer

ATCC Deposit No. 209064**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209064

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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429

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2709</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209065</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<input checked="" type="checkbox"/> For receiving Office use only This sheet was received with the international application RO/US 09 MAR 2000 Authorized officer: <u>Joelanda Harco</u> <u>PCT/Int'l Appl Processing Div.</u> <u>(703) 305-3370</u>	<input type="checkbox"/> For International Bureau use only This sheet was received by the International Bureau on: Authorized officer: _____
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ATCC Deposit No. 209065**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209065

DENMARK

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SWEDEN

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NETHERLANDS

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432

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209066
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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RO/US 06 MAR 2000 Authorized officer: Yolande Harrod PCT/Int'l Appl Processing Div. (703) 305-3670	Authorized officer

ATCC Deposit No. 209066**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2
ATCC Deposit No. 209066

DENMARK

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SWEDEN

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NETHERLANDS

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435

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) <p style="text-align: center;">10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p>	
Date of deposit <p style="text-align: center;">20 May 1997</p>	Accession Number <p style="text-align: center;">209067</p>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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RO/US J3 MAR 2000
Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. (700) 385-3670

For International Bureau use only
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Authorized officer

ATCC Deposit No. 209067**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2

ATCC Deposit No. 209067

DENMARK

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SWEDEN

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NETHERLANDS

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438

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209068
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
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<input checked="" type="checkbox"/> This sheet was received with the international application
Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. (703) 305-3870

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Authorized officer

ATCC Deposit No. 209068**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2

ATCC Deposit No. 209068

DENMARK

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SWEDEN

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NETHERLANDS

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441

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209069
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<p>For receiving Office use only</p> <p><input checked="" type="checkbox"/> This sheet was received with the international application</p> <p>RO/US 05 MAR 2000</p> <p>Authorized officer Andrea Harrod PCT/Int'l App. Processing Div. (703) 305-3879</p>	<p>For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
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ATCC Deposit No. 209069**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209069

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

444

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>12 January 1998</u>	Accession Number <u>209579</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application <u>RECEIVED 02 MAR 2000</u>	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer <u>[Signature]</u>	Authorized officer <u>[Signature]</u>

ATCC Deposit No. 209579**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209579

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

447

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 12 January 1998	Accession Number 209578
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
RO/US 03 MAR 2000	
Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. 703 305 3670	Authorized officer

ATCC Deposit No. 209578**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209578

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

450

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 16 July 1998	Accession Number 203067
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer RO/US 08 MAR 2000 PCT Internat'l Appl Processing Div 703A 305-3870	Authorized officer

ATCC Deposit No. 203067**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203067

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

453

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <p>American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) <p>10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p>	
Date of deposit <p>16 July 1998</p>	Accession Number <p>203068</p>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<input checked="" type="checkbox"/> For receiving Office use only This sheet was received with the international application RO/US 03 MAR 2000 Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. 7031 305 3020	<input type="checkbox"/> For International Bureau use only This sheet was received by the International Bureau on: Authorized officer
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ATCC Deposit No. 203068

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203068

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

456

Applicant's or agent's file reference number	PA103PCT	International application
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> .	
B. IDENTIFICATION OF DEPOSIT	
Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 1 February 1999	Accession Number 203609
C. ADDITIONAL INDICATIONS (leave blank if not applicable)	
This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer Yolanda Harrod PCT/International Appl Processing Div. (703) 305-6674	Authorized officer

ATCC Deposit No. 203609**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203609

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

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459

Applicant's or agent's file reference number	PA103PCT	International application?
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 1 February 1999	Accession Number 203610
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<input checked="" type="checkbox"/> For receiving Office use only
<input type="checkbox"/> This sheet was received with the international application
RO/US 08 MAR 2000
Authorized officer Volanda Harrod
PCT/Internat'l Appl Processing Div.
(703) 305-3670

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<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer

ATCC Deposit No. 203610**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203610

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

462

Applicant's or agent's file reference number	PA103PCT	International application f
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 17 November 1998	Accession Number 203485
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<input checked="" type="checkbox"/> For receiving Office use only This sheet was received with the international application RO/US . 08 MAR 2000 Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Off. (703) 305-3670	<input type="checkbox"/> For International Bureau use only This sheet was received by the International Bureau on: Authorized officer
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ATCC Deposit No. 203485**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2
ATCC Deposit No. 203485

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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465

Applicant's or agent's file reference number	PA103PCT	International application ?
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 18 June 1999	Accession Number PTA-252
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application RO/US 03 MAR 2000 Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div.	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
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ATCC Deposit No. PTA-252**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2

ATCC Deposit No. PTA-252

DENMARK

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SWEDEN

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NETHERLANDS

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468

Applicant's or agent's file reference number	PA103PCT	International application N°
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 18 June 1999	Accession Number PTA-253
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application 80/US 03 MAR 2000 Authorized officer Volanda Harrod PCT/Internat'l Appl Processing Div. (703) 305-3670	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
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ATCC Deposit No. PTA-253**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2**ATCC Deposit No. PTA-253****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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471

Applicant's or agent's file reference number	PA103PCT	International application #
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 22 December 1999	Accession Number PTA-1081
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application RO/US 03 MAR 2000 Authorized Valenda Harrod PCT/Internet Appl Processing Div. (703) 305-3670	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
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ATCC Deposit No. PTA-1081**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2

ATCC Deposit No. PTA-1081

DENMARK

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NETHERLANDS

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What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
 - (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (c) a polynucleotide encoding a polypeptide fragment of a polypeptide encoded by SEQ ID NO:X or a polypeptide fragment encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (d) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (e) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (f) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X, having biological activity;
 - (g) a polynucleotide which is a variant of SEQ ID NO:X;
 - (h) a polynucleotide which is an allelic variant of SEQ ID NO:X;
 - (i) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
 - (j) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide

sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a protein.

5

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X.

10

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X.

15

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

20

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

25

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

30

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.
11. An isolated polypeptide comprising an amino acid sequence at least
5 95% identical to a sequence selected from the group consisting of:
- (a) a polypeptide fragment of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
 - (b) a polypeptide fragment of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone, having biological activity;
 - 10 (c) a polypeptide domain of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
 - (d) a polypeptide epitope of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
 - (e) a full length protein of SEQ ID NO:Y or of the sequence encoded by the
15 cDNA included in the related cDNA clone;
 - (f) a variant of SEQ ID NO:Y;
 - (g) an allelic variant of SEQ ID NO:Y; or
 - (h) a species homologue of the SEQ ID NO:Y.
- 20 12. The isolated polypeptide of claim 11, wherein the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.
13. An isolated antibody that binds specifically to the isolated polypeptide
25 of claim 11.
14. A recombinant host cell that expresses the isolated polypeptide of claim 11.
- 30 15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

5 16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

10

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

15 (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

20 (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

25 20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

30

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.
22. A method of identifying an activity in a biological assay, wherein the method comprises:
- 5 (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;
- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.
- 10 23. The product produced by the method of claim 20.

SEQUENCE LISTING

<110> Craig Rosen,
Steve Ruben

<120> Human Breast and Ovarian Cancer Associated Gene Sequences and
Polypeptides

<130> PA103PCT

<140> Unassigned

<141> 2000-03-08

<150> 60/124,270

<151> 1999-03-12

<160> 846

<170> PatentIn Ver. 2.0

<210> 1

<211> 1913

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (944)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1418)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1908)

<223> n equals a,t,g, or c

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gataatggac ctccttggag accgagttaa gctggagagg cctgtgatct acattgacca 180
gacaagagaa aatgtccttg tggagaccct aaaccatgag atgtatgagg ctaaatatgt 240
gattagtgtc attcctccta ctctgggcat gaagattcac ttcaatcccc ctctgccaat 300

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gatgagaaac cagatgatca ctctgtgtgcc tttgggttca gtcacatcaagt gtatagttta 360
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agaagctcca gttgcctaca cgttggatga taccaaacct gaaggcaact atgctgccat 480
aatgggattt atcctggccc acaaagccag aaaactggca cgtcttacca aagaggaaaag 540
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aataaaagtt gattgacat aaaaaaaaaa aaaggggggg ccgccangg ggg 1913

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<210> 2

<211> 1425

<212> DNA

<213> Homo sapiens

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<221> misc feature

<222> (790)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (842)

<223> n equals a,t,g, or c

<400> 2

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aaagacaaaa tgtggcttat tttaggatct gttttttcat cgaggctctg ggtatccttt 180
caaagatagt garaagcaga cactgtcctt tgtgcagctc tggtagctcc tgcccactgc 240
tgtcacttca agccactggc aatgcttctg tcctcgtgtc ttggaggaaa atcacctggg 300
gggagggggc ttcttgtggt aagagcaagt gcaggatga aatgcgaaga ttgccccagc 360
taaaagtgga caagtccgct ttgtgagatg aatacttcct gagaaacttg acaagtatct 420

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ctccatttta ccattatgaa aactatcatt aaaaaaaca gtttagatgc cttctccttt 480
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ttgtttgaac ttccgtcttt agctgataga ttctcaaata tccttgattt tggatgttca 600
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<210> 3

<211> 354

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (246)

<223> n equals a,t,g, or c

<400> 3

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gtattatttg caaggagtca aagatgatgt cttttcccag aggcattgaac cttagaaatg 120
ctttcgatgg ggatgtttct gtaacactgt gttattctgg atcttcaaata aatagcaaaag 180
ccaattactc taaatgtaaa atttttctat tcccaagggt cacttttggt tggtaggttt 240
tcacgntttt aaatactggt taatggaaga aaaatacgta gccaggcgtg gtggctcaca 300
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<210> 4

<211> 514

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (502)

<223> n equals a,t,g, or c

<400> 4

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tgcagaagtc gcacaagacc cgcaaccagc acaggacgag gggatcctgc cctcgggcag 120
acggggcacg gcgagaggtc ctgccagata agctgtaggg gctcaggcca cctccctgc 180
cacgtggaga cgcagaggcc gaacccaaac tggggccacc tctgtaccct cacttcaggg 240

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cacctgagcc accctcagca ggagctgggg tggccctga gctccaacgg ccataacagc 300
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gggttgggtt agttgcctag aaccctgcc agggctgggg gtgagaagg gagtcattac 420
tccccattac ctaggggccc tccaaaagag tccttttaaa taaatgagct atttaggtgc 480
wraaaaaaaa aaaaaaaaaac cncggggggg gcc 514

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<210> 5

<211> 2035

<212> DNA

<213> Homo sapiens

<400> 5

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atactgtcaa aacataagca aatgtcgtcg tgtgttgatg gctcaacatt ttgatgaagt 180
atggaactca gaagcatgta acaaaatgtg cgrtaactgc tgtaaagaca gtgcatttga 240
aagaaagaac ataacagagt actgcagaga tctaatacag atcctgaagc aggcagaggg 300
amctggaatg gaaaaactca ctcccattgg aaactggatt gattcttggr tgggaaagg 360
tgcagcaaaa ctgagagtag cagggtgtgt ggctcccaca ctctctctg aagatctgga 420
gaagattatt gcacacttts taatacagca gtatcttaaa gaagactaca gttttacagc 480
ttatgctacc atttcgtatt tgaaaatagg acctaaagct aatcttctga acaatgaggc 540
acatgctatt actatgcaag tgacaaagtc cacgcagaac tctttcaggg ctgaatcgtc 600
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<210> 6

<211> 1196

<212> DNA

<213> Homo sapiens

<220>
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 <222> (157)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (998)
 <223> n equals a,t,g, or c

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 ccagaatgga ctggagtga ggcgtgtcta gagtgtgggc tggctgtgtg gctggaaagc 1140
 tggggacagg ttgatggtaa taaactgctc aatgaccagt gaaaaaaaaa aaaaaa 1196

<210> 7
 <211> 624
 <212> DNA
 <213> Homo sapiens

<400> 7
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 tctatagcat ttgatgttac aactctaagc gtagtccaag gacatttaaa ttgacaagtt 180
 accagttaaa gaatttagaa tatattagat cccatctagt attatatatt ttttctagtt 240
 gatcattgag cagtaaatac caaatactcg attagaaggt aatttttaca ttgttttgaa 300
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<210> 8
 <211> 301
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (289)
 <223> n equals a,t,g, or c

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 c 301

<210> 9
 <211> 686
 <212> DNA
 <213> Homo sapiens

<400> 9
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 cagctgttca tccatttcgt gttttttcct gtcaaacatt aatccagcaa atatatgagg 180
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 catactttaa aagatcaaaa aaaaaa 686

<210> 10
 <211> 397
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (379)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (394)
 <223> n equals a,t,g, or c

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cygggcgagg agcgctcta caacccttc ctgcgggtgg cgtgagtatg gctgttgctc 180
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<210> 11
<211> 563
<212> DNA
<213> Homo sapiens

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<220>
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<222> (10)
<223> n equals a,t,g, or c

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<220>
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<222> (13)
<223> n equals a,t,g, or c

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<220>
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<222> (37)
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<220>
<221> misc feature
<222> (510)
<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (562)
<223> n equals a,t,g, or c

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actgtgggct ctggagagag gagggggcaa tagagctagg rattaaggaa tcagttgwtg 480
aaaatgkgt atattttatc ccccattaan taactggact aggggaaggga ctaaaaggcc 540
agaaaagggg atgaaaaaaa ant 563

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<210> 12
 <211> 443
 <212> DNA
 <213> Homo sapiens

<400> 12
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 gtcacgcggc acgtggactc cggaaagtcc accaccacgg gccacctcat ctacaaatgc 180
 ggaggtattg acaaaaggac cattgagaag ttcgagaagg aggcggctga gatggggaag 240
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 accatcgaca tctccctctg gaagttcgag accaccaagt actacatcac catcatcgat 360
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 gcagtgtga tcgtggcggc ggg 443

<210> 13
 <211> 2438
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (117)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (681)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (713)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (2413)
 <223> n equals a,t,g, or c

<400> 13
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gaggcctggc caatgcggcc nactttcctg agctgtcgct gcctccatgg canagccarg 720
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<210> 14

<211> 2347

<212> DNA

<213> Homo sapiens

<400> 14

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aagagaaggt gcgtatagca gaaaattca tcattcatgc ccctcctgga gaatttaatg 180
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gaaaaaa 2347

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<210> 15

<211> 2006

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (862)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1006)

<223> n equals a,t,g, or c

<400> 15

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gcccagcatg taaacaagag aaagacgata aggaagagaa gaaagacgca gctgagcaag 180
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caaagccttc tactaccca acttcacctc ggcctcaagc acaacctagc ccatctatgg 300
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ggcaagacca gcatcatcag agtgccatga tgcaaccagc gtcagcagcg ggcccaccga 540
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ttatttataa atcaagttt atgaggtgat cactgtctac agtggttcaa cttttaagtt 1920
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ataaaaaaag ttttaaaaac tgaaaaa
2006

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<210> 16

<211> 986

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (613)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (932)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (933)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (985)

<223> n equals a,t,g, or c

<400> 16

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caaaaccagc tgccacgata cgcatcgtgc agggactggg agtgatgcct cccaaagcag 180
gccagaccat caccgttgca acccacgcca agcaaggggc ctcggtggcc agtgggtctg 240
gaactgtcca tacttcagcg gtgtccttac ccagtatgaa tgctgctgtg tccaagactg 300
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gcggcaggtc cctgtcagca ccacggttgt gtccacgtcc caggctggga agttgcctac 420
acggatcaca gttccctctc ctgtgatcag ccagccaatg aagggaaga gcgtgggtcac 480
agccccatc atcaaaggca accttggagc caacctcagt gggttgggcc gcaacatcat 540
cctcacaact atgccagcag gactaagct cattgctggc aataagcctg ttagtttcct 600
cactgctcag canttgagc agcttcagca gcaaggtcag gccacacagg tgcgcatcca 660
gactgtccct gcatcccatc tccaacaggg aacagcttct ggctcctcca aagcagtctc 720
cactgttgtt gtgactacag ctccgtctcc taaacaggca cctgagcaac aatgattatg 780
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gagttgcatc attgttttaa gctgcctgtt caaggcagcc aggcgagggt gatggcaacg 900
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<210> 17

<211> 1589

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (25)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (555)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (809)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1033)

<223> n equals a,t,g, or c

<400> 17

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tgccccccac ccagcctaa gatgaagagg atcggaggct tgtcagagct gggaggggtt 120
ttcgaagctc agcccacccc cctcattttg gatataggtc agtgaaggcc caggagagg 180
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gggaaatggc ttgaagccaa gtcagctttg ccttccacgc tgtctccaga cccccacccc 360
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gagtcagggt tgggggtcgt ggaaaggggt ctgcttccct ctgcctgtcm ctctcaggca 480
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agaaaagaaaa ataaaaaaaa aaaaaaaaaa 1589
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<210> 18

<211> 846

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (746)

<223> n equals a,t,g, or c

<400> 18

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gcgcccattg tgccactgca ccagaagcag agccgcacat ccccatcca gaagccgcgg 120
ggcstcgacc ctgtggagat cctgcaggag cgcgagtaca ggctgcaggc tcgcatcgca 180
caccgaattc aggaacttga aaaccttccc ggggtccctg ccggggattt gcgaacccaa 240
gcgaccattg agctcaaggc cctcaggctg ctgaaattcc agaggcagct gcgccaggag 300
gtgggtggtg gcatgcggag ggacacagcg ctggagacag ccctcaatgc taaggcctac 360
aagcgcasaa gcgccagtc ctgcgcgagg cccgcacac tgagaagctg gagaagcagc 420
agaagatcga gcaggagcgc aagcgccggc agaagcacca ggaatacctc aatagcattc 480
tccagcatgc caaggatttc aaggaatatc acagatccgt cacaggcaaa atccagaagc 540
tgaccaaggc agtggccacg taccatgcca acacggagcg ggagcagaag aaagagaacg 600
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agctcatcga ccagaagaag gacaagcgcc tggcctacct cttgcagcag acagacgagt 720
acgtggctaa ctcacggagc tggtgncggc acaaggctgc ccaggtcgcc aaggagaaaa 780
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cggatg 846
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<210> 19
<211> 2192
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (115)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2106)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2118)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2143)
<223> n equals a,t,g, or c

<400> 19
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aacgacagaa agcacacaat gcgaagatga ggagctggag cacttgagggt tgcttgaacc 480
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2192

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<210> 20

<211> 1011

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (54)

<223> n equals a,t,g, or c

<400> 20

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gacagtttta cgcattccr tccactcccg attccttcat ggatccggcg tctgactttt 180
acagaggtcc aatcacgcgg acccagaacc ccatggtgac cgggacctca gtcctcggcg 240
ttaagttcga gggcggaagt gtgattgccg cagacatgct gggatcctac ggctccttg 300
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aaaaaggtgt tgaaatagag ggaccattgt ctacagagac caactgggat attgccaca 840
tgatcagtgg ctttgaatga aatacagatg cattatccag aactgaagtt gccctacttt 900
taactttgaa cttggctagt tcaaagatag actcttcttt tgtaaagtaa ataaattctt 960
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<210> 21

<211> 2019

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2003)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2007)

<223> n equals a,t,g, or c

<400> 21

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<210> 22

<211> 2022

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1588)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1615)

<223> n equals a,t,g, or c

<400> 22

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tgtgacgcca ctcaccttta ctgaggtgca cgagggccgt gctgacatca tgatcgactt 180
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gctaccactt gagtctcagc ccagatgact gcaggggctt tcaaacctta tatggccagc 480
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tgtgtgtaca gtgtgtataa accttcttct tctttttttt ttttaaaactg aggattgtca 1920
ttaaacacag ttgttttcta aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1980
aaaaaaaaaa aaaaagggcg gccgctcgcg atctagaact ag 2022
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<210> 23

<211> 1126

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1126)

<223> n equals a,t,g, or c

<400> 23

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gtaaacgtgt gacgggggaa agccaaggtc tggagaagct cccaggaaca ayygatggcc 180
ttgcagcaact cacacaggac ccccttcccc taccctctcc tctctgccgc aatacaggaa 240
ccccagggg aaagatgagc ttttctaggc tacaattttc tcccaggaag ctttgatttt 300
taccgtttct tccctgtatt ttctttctct actttgagga aaccaaagta accttttgca 360
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tctcctccaa gacactgttg acttggtcac cagctcctcc cttgttctct aagttccact 480
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caggctcttg agctgagcct ctcacctgta ctcttccgaa aaatcctctt cctctgaggc 720
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gtgatactga aacacaaaaa aaaaaaaaaa aaaaaaaaaa aaaaan 1126
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<210> 24

<211> 2598

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2304)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2500)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2533)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2553)

<223> n equals a,t,g, or c

<400> 24

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raggtttaaa garactacca gaccattttc caatgaatgt cttggtacca ccagaccctg 120
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agttcctatt gattcatcag attttgcatt ggatattcgc atgcctgggg ttacacctaa 180
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gattgacttc aagcctcgag ccagcatgga tactgtccat cacatgttac tttttggatg 300
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tggaattcaga gttggaggag agactggaag taaatacttt gtactacagg tacactatgg 480
ggatattagt gcttttagag ataataacaa ggactgttct ggtgtgtcct tacacctcac 540
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<210> 25

<211> 411

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (358)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (368)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (381)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (387)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (392)

<223> n equals a,t,g, or c

<400> 25

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ctctgagctc caggtcacaa tgcacgacac ccggggccgc agtccccat accagctnng 360
actyccangg ggcgcctggt ngctggnytg anggccark tggcgacgag.c 411
```

<210> 26

<211> 657

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (634)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (652)

<223> n equals a,t,g, or c

<400> 26

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cagccccctct tcccttcctc cattgcacat gaacatatgt ccatccatat atattcatca 180
gaatgttaat ttattttgct ccctctgtta ggtccatttt ctaagggttag aagaggcaag 240
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tggtagggat gaggtctgat aagaacccag ggtggagagg gagactcctg ggcagccgtt 300
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tctgcacgtt gctgaaggtc caggcttgcc tcaagttcca tgcttgagca ataaagtggg 600
aacaataaaa cctgggaaaa aaaaaaagg gggncgttct aaaggatccc cnagggg 657

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<210> 27

<211> 1903

<212> DNA

<213> Homo sapiens

<400> 27

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agccaccatg aaggtggggg aggtgtgcca catcacctgc aaaccagaat atgcctacgg 180
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<210> 28

<211> 1333

<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (1311)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1313)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1319)
<223> n equals a,t,g, or c

<400> 28
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tggccatctt cgggcccccc aacacctact acgagggcgg ctacttcaag gcgcgcctca 180
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<210> 29
<211> 1327
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (573)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1307)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1325)
<223> n equals a,t,g, or c

<400> 29
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aatacaaggc cgccgcgcgc gaggccggcc gcgccatgca cctgatgaag aagcgggaga 120
agcagcgcca gcagatggag cagatgaagc agcgcacgcs ggaggagAAC atcatgaaat 180
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tcagctactg ggatggctct gggcaccggc ggacagtcaa gatgagaaag ggcaacacca 720
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cgtgtcctgc cctgccaca tcagtgaactg ctttattctt ttccaataaa gaagtgcacg 1260
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agggngg 1327

<210> 30
<211> 709
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (696)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (701)
<223> n equals a,t,g, or c

<400> 30

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aattcccggg ttcgaccac gcgtccggaa aactgcagct tccttctcac cttgaagaat 60
aatcctagaa aactcacaaa atgtgtgatg cttttgtagg tacctggaaa cttgtctcca 120
gtgaaaactt tgatgattat atgaaagaag taggagtggg ctttgccacc aggaaagtgg 180
ctggcatggc caaacctaac atgatcatca gtgtgaatgg ggatgtgatc accattaaat 240
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cactgcagat gacaggaaaag tcaagagcac cataacctta gatgggggtg tcctgggtaca 360
tgtgcagaaa tgggatggaa aatcaaccac cataaagaga aaacgagagg atgataaact 420
gggtggggaa tgcgtcatga aaggcgtcac ttccacgaga gtttatgaga gagcataagc 480
caagggacgt tgacctggac tgaagtccgc attgaactct acaacattct gtgggatata 540
ttgttcaaaa agatattgtt gttttccatg atttagcaag caactaattt tctcccaagc 600
tgattttatt caatatgggt acgttggtta aataaacttt ttttagattt aaaaaaaaaa 660
aaaaaaaaacc ycgggggggg gcccgggtacc caattngccc nttaggggg 709

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<210> 31

<211> 1108

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (389)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (397)

<223> n equals a,t,g, or c

<400> 31

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ccaaacaact tttaattgat ccagaagatg atgtaagaga taatatTTTA aaatatgatg 120
aagaaggtgg aggagaagaa gaccaggact atgacttgag ccagctgcag cagcctgaca 180
ctgtggagcc tgatgccatc aagcctgtgg gaatcygacg aatggatgaa agaccatcc 240
acgccgagcc ccagtatccg gtccgatctg cagccccaca ccctggagac attggggact 300
tcattaatga gggccttaaa gcggtgaca atgacccac agctccacca tatgactccc 360
tgtagtggtt tgactatgaa ggcagtggnt cactgntgg gtccttgagc tcccttaatt 420
cctcaagtag tgggtggtgag caggactatg attacctgaa cgactggggg ccacggttca 480
agaaacttgc tgacatgtat ggtggagggtg atgactgaac ttcagggtga acttggtttt 540
tgacaagta caaacaattt caactgatat tcccaaaaag cattcagaag ctaggcttta 600
actttgtagt ctactagcac agtgcttgct ggaggctttg gcataggctg caaaccaatt 660
tgggctcaga gggaatatca gtgatccata ctgtttggaa aaacactgag ctcagtaca 720
cttgaatttt acagtacaga agcactggga ttttatgtgc ctttttgtag ctttttcaga 780
ttggaattag ttttctgttt aaggctttaa tggtagtgat ttctgaaacg ataagtaaaa 840
gacaaaatat tttgtggtgg gagcagtaag ttaaaccatg atatgcttca acacgctttt 900
gttacattgc atttgctttt attaaaatac aaaattaaac aaamaaaaaa actcatggag 960
cgattttatt atcttggggg atgagacat gagattggaa aatgtacatt acttctagtt 1020
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```

1108

<210> 32

<211> 526

<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (502)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (524)
<223> n equals a,t,g, or c

<400> 32
gaatttttca ttatgttgct ttgaaattt gatgcattcc tccattttac tttattattg 60
tacacattta acacacagta gcaaattttg aacgatgtga ttgatataac ctaacaaatc 120
tgagccagtt attattagag ttgcagaata gaaacttgaa gtgctaaatg gaataatcca 180
aaggaaattt tttaaattgca ggttctagct gaaaaattca actataagaa aattgtattt 240
atataacatt tactattttt gaagactagt gagatttctg taataatttt aattccttta 300
aaagtgaag cttgttgtaa agatattttc tttttgttat tagaaggaaa tacaagaga 360
aaaatttctt tctttcatgg ggcatttgat aatttcagtc tttgacgatt tgtaagccta 420
gaatatacta agctgaataa cagctctttg gcctcagaat tttccagtag ccagtawttc 480
yggattaact aagttggaaa cncytattag gaacctccag tggnga 526

<210> 33
<211> 555
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (494)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (521)
<223> n equals a,t,g, or c

<400> 33
ccggaccctg caccagcga ctgggccccg cgcgcgccct ccgcgagggg ggaggcggcg 60
gctgtgtgcg cagggcccg caccggactg ggaccctggc gtccctccag gccttgctc 120
ctgcgggags acagtttggc ttactttctc tgacccagc ctcggccgta aagtgaaga 180
gaccggacca gcttcagctt tcggactctg gttcttgat cgtgtcctct cccctcgc 240
gccctcttc cccaatctga gccattkcag gcctctgcct gckgccccct ctctcctc 300
gatcgggtcc ccagagccac catctcctga gcctccacc ccgctgcctg ggccctgtg 360
ttgctgggcc tcccacctca aggaggggaa ggttgtagc cccgaaccgg tggagcaatg 420
ccctgtctgg cctccaaaac caaaataaaa ctgggtcact ttacaaaaaa aaaaaaaaaa 480
aaggggcccc gaanaccgga ccggtacctg caggcgtacc ngtttcccta tagtgagttg 540
tattagcgtt gcata 555

<210> 34
 <211> 347
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (288)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (328)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (335)
 <223> n equals a,t,g, or c

<400> 34
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 gggggtggag gcggctcctg cratctaaag ggacttgaga ctctcaccgg ccgcgcgcca 120
 tgagggccct gtgggtgctg ggcctctcct gcrtcctget gaccttcggg tcgggtccgar 180
 ctgaygatga agtcgatgtg gatggtacag tggaagagga tctgggtaaa agtagagaag 240
 gttcaaggac agatgatgaa gtagtacaga gagaggaaga agctattnca gttggatgga 300
 ttaaatgcat cccaaataag agaacttnag agagnaagtc cagaaaa 347

<210> 35
 <211> 750
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (701)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (731)
 <223> n equals a,t,g, or c

<400> 35
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 catgggttca acttggacac tgaaaacgca atgaccttcc aagagaacgc aaggggcttc 180
 gggcagagcg tgggtccagct tcagggatcc aggttggtgg ttggagcccc ccaggagata 240
 gtggctgcca accaaagggg cagcctctac cagtgcgact acagcacagg ctcatgagag 300
 cccatccacc tgcaggtccc cgtggaggcc gtgaacatgt ccctgggcct gtccctggca 360
 gccaccacca gccccctca gctgctggcc tgtggtccca ccgtgcacca gacttgcagt 420

gagaacacgt atgtgaaagg gctctgcttc ctgtttggat ccaacctacg gcagcagccc 480
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actgtgatgg agcaattaaa aaagtccaaa acctgttctt ctttgatgca gtactctgaa 660
gaattccgga ttcactttac ttcaaagagt tccagaacaa ncctaaccga agatcactgg 720
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<210> 36

<211> 1291

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (29)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (298)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (695)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (795)

<223> n equals a,t,g, or c

<400> 36

aagaaaaatg tactacgcct gtcctgtang aagctgaaga tttttgcaat gcccatgcag 60
gatatacaga tgatcctgaa aatggtgcag ctggactcta ttgaagattt gggaagtgc 120
ttgtacctgg aagctaccca ccttggcgaa attttctcct tacctgggcc agatgattaa 180
tctgcgtaga ctccctctct cccacatcca tgcattctcc tacatttccc cggagaagga 240
agagcagtat atcgcccagt tcacctctca gttcctcagt ctgcagtgcc tgcagctnct 300
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gaaccctctg gaaaccctct caataactaa ctgccggcct tcggaagggg atgtgatgca 420
tctgtcccag agtcccagcg tcagtcagct aagtgctctg agtctaagtg gggatcatgct 480
gaccgatgta agtcccagcg ccctccaagc tctgctggag agagcctctg ccaccctcca 540
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cctgagccac tgcctccagc ttacaacctt aagcttctac gggaattcca tctccatata 660
tgccttgcaag agtctcctgc agcacctcat cggngtgagc aatctgacct acgtgctgta 720
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cctgtgcccc tgtttcatgc ctaatarctg ggtgcacata tcaaagtctt cattctgcat 960
acttgacac taaagccagg atgtgcatgc atcttgaaagc aacaaagcag ccacagtttc 1020
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atgttcagtg agggaaaaaa ggggagttgg ggataggcag atgttgactt grggagktaa 1140
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agawtctggc ttgggaagta catgtaggag ttaatccctg tgtagactgt tgtaaagaaa 1260
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<210> 37
<211> 1535
<212> DNA
<213> Homo sapiens

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<220>
<221> misc feature
<222> (1413)
<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (1526)
<223> n equals a,t,g, or c

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<400> 37
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tgcacccagg ccacgtgctg cccgacgagg agctgcagtg ggtgttcgtg aatgcgggtg 180
gctggatggg cgccatgtgc cttctgcacg cctcgtctgc cgagtatgtg ctgctcttcg 240
gcaccgcctt gggctcccg cggcactcgg ggcgctactg ggctgagatc tcggatacca 300
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caggggagac ggtagtacac gggcctggtg aggaacacgc tgtggagtgg gggccaaaca 420
catggatggt ggagtacggc cggggcgctc tccatccac cctggccttc gcgctggccg 480
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acacacacaa cacatacaca cacacacaca canacacata tcacagtttt cacacagccc 1440
ctgctgcatt ctctgtccat ctgtctgttt ctattaataa agatttggtg atctgttcca 1500
aaaaaaaaaa aaaaaaaaaa aaaaangggg gggct                               1535

```

```

<210> 38
<211> 295
<212> DNA

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<213> Homo sapiens

<400> 38

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tgcattggcg gcggtcaggg aattgcgatg gtgattgaac ggttgaatta atcaataaaa 120
acacccgata gcgaaagtta tcgggtgttt tcttgaacat cgacggcgaa ggtaacccca 180
ttaatcacca gtcaaaaactt ttcaccagcg tcaactcgcca gcattacgca tcggtacaat 240
aaatgtttcc tgtttctcat tgaccgatcc ttcacggtg atcagcgta ttggg 295
```

<210> 39

<211> 1300

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (641)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1297)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1298)

<223> n equals a,t,g, or c

<400> 39

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gcggaactggc agggggcagg gaagctcaaa gatctgggggt gctgccagga aaaagcaaatt 60
tctggaagtt aatggttttt agtgattttt aaatccttgc tggcgagag gcccgctct 120
ccccggtatc agcgcttccct cattctttga atccgcggct ccgcggtctt cggcgctcaga 180
ccagccggag gaagcctggt tgcaatttaa gcgggctgtg aacgcccagg gccggcgagg 240
gcggggccga ggcgggccat tttraataaa gaggcgtgcc ttccaggcag gctctataag 300
traccgccc gcgagcgtg cgcgckttgc aggtcactgt agcgggactt cttttggttt 360
tctttctctt tggggcacct ctggactcac tccccagcat gaaggcgtg agcccggtgc 420
gcggctgcta cgaggcgggtg tgctgcctgt cggaacgcag tctggccatc gcccggggcc 480
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aaatcctaca gcgcgtcatc gactacattc tcgacctgca ngtagtcctg gccgagccag 660
cccttgacc ccctgatggc cccacacctc ccatccagac agccgagctc gctccggaac 720
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cagaacgcag gtgctggcgc ccgttctgcc tgggacccc ggaacctctc ctgccggaag 840
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gagctagctc tgccaccag ctgggcgagc tcacctgct cccacccac cccaagttc 1020
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caatgcgatg tatattaaac tttttataaa agttaacatt ttgcataata aacgattttt 1260
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aaacaaaaaa aaaaaaaaaa aagggggggcc gccctannng

1300

<210> 40

<211> 215

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (210)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (213)

<223> n equals a,t,g, or c

<400> 40

cagaaacaga agttcacact aacagagtat ggttttaatt ttcctttgaa tgaaaaggat 60
 agaaagataa aattgtgtat tgtaacatg taaataaaat tggagctaata ttgaaactag 120
 cttctcaata acttcacatt tctagagact cattacctgt gggcttgctm aacctggact 180
 atttggccaa atwgggttga taaaaaaggn atntt 215

<210> 41

<211> 474

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (85)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (216)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (374)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (449)

<223> n equals a,t,g, or c

<400> 41

tcgacccacg cgtccgggag actacggtaa aggcgcgcgc acgcagccaa catgccggtg 60
 gcccgagct gggtttgcg caagnctacg tgaccctcg gaggcccttt gagaagtcgc 120

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ggctcgacca agagctgaag ctgataggcg agtacgggct ccggaacaaa cgtgaggtgt 180
ggaggggtcaa gttcaccctg gccaaagatcc gcaagnccgc gcgggarctg ctgacgctgg 240
acgagaagga cccgcggcgc ctgtttgagg gcaatgcctt gcttcggcga ctggtgcgca 300
ttggagtgtc ggacgagggc aagatgaagc tggattatat cctgggtctg aagatgagga 360
ttcttgga grontctgca gaccaggtt tttcaagctg gggttgcca atccatccac 420
catgccctgt gctgatccgc caggccacnc aggtccgaaa gcaagtgtg aaca 474

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<210> 42

<211> 425

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (375)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (403)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (418)

<223> n equals a,t,g, or c

<400> 42

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cctcgcccttc gatgaatatg ggcgcccttt cctcatcatc aaggatcagg atcgcaagtc 60
tcgtcttatg ggactggagc tctcaagtct catatcatgg cggcaaaggc ttagcaaat 120
accatgagaa catcacttgg accaaatgga cttgataaaa tgatggtgga caaggacggc 180
gacgtgacgg tcacaaacga cgtgcccacg attctgagca tgatggatgt cgatcaccag 240
attgccaaagc tgatggtgga gctgtccaaa tcccaggatg atgaaatcgg agatggggac 300
cacgggggtg gttgtcctgg ccggcgccct gctggaagga ggccgagcag ctgctggacc 360
gcggcattca mccgntcagg atcgccgacg gttacgagca ggntgcccgc attggccntc 420
gagca 425

```

<210> 43

<211> 1187

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (33)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (41)

<223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1149)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1156)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1160)
 <223> n equals a,t,g, or c

<400> 43
 tgtgggaact ggtgggtccc ccgggctggc agnaattggg nacgcgggtc gcggttcttg 60
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 aagaccatca ccctcgaggt tgagcccagt gacaccatcg agaattgtcaa ggcaaagatc 180
 caagataagg aaggcatccc tcctgaccag cagaggctga tctttgctgg aaaacagctg 240
 gaagatggkc gcaccctgtc tgactacaac atccagaaaag agtccaccyt gcacctggtr 300
 ctccgtctca gaggtgggat gcaaatcttc gtgaagacac tcactggcaa gaccatcacc 360
 cttgaggtcg agcccagtga cacyatcgag aacgtcaaag caaagatcca rgacaaggaa 420
 ggcattcctc ctgaccagca gaggttgatc tttgccggaa agcagctgga agatgggctg 480
 accctgtctg actacaacat ccagaaagag tctaccctgc acctgggtgct ccgtctcaga 540
 ggtgggatgc agatcttcgt gaagaccctg actggtaaga ccatcacyst cgargtggag 600
 ccgagtga caattgagaa tgtcaaggca aagatccaag acaagggaagg catccctcct 660
 gaccagcaga ggttgatctt tgctgggaaa cagctggaag atggacgcac cctgtctgac 720
 tacaacatcc agaaagagtc caccctgcac ctggtgctcc gtcttagagg tgggatgcag 780
 atcttcgtga agaccctgac tggtaagacc atcactctcg aagtggagcc gactgacacc 840
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 accctgactg gtaagaccat cacyctcgaa gtggagccga gtgacaccat ygagaatgtc 1080
 aaggcaagat ccagacaagg aaggcatcct cctgaccagc agargttgat tttgctggga 1140
 aaarcttgna aatggncgan cccttttgat taaaatcccc aaagtcc 1187

<210> 44
 <211> 515
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (217)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (465)

<223> n equals a,t,g, or c

<400> 44

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ctgcagtacc gtccgaattc ccgggtcgac ccacgcgtcc ggtttgagcc gtcgtgcttc 60
accggtctac ctgcctagca tgcggggccg cggcaagact ggcggaagg cccgcgcaa 120
ggccaagtcg cgtcgtcgc gcgcccgcct ccagttccca gtgggcccgtg tacaccggt 180
gctgcggaag ggccactacg ccgagcgcgt tggcgcnngc rcgccagtgt acctggcggc 240
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caagaagacg cgaatcatcc cccgccacct gcagctggcc atccgcaacg acgaggagct 360
caacaagctg ctgggcccgc tgacgatcgc ccagggaagg cgtctgccc aacatccagg 420
ccgtggttg tgcccaagaa gaccagcgc accgtggggc cgaangccct tcggggggca 480
agaaagggca accaaggctt cccaaggagt actaa 515
```

<210> 45

<211> 1499

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1476)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1492)

<223> n equals a,t,g, or c

<400> 45

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gcgagtgcgc gctcctcctc gcccgccgct aggtccatcc cggcccagcc accatgtcca 60
tccattcag ctccccggca tccgcgaggt caccattaac cagagcctgc tggccccgct 120
gcggtggac gccgaccctt cctccagcg ggtgcgccag gaggagagcg agcagatcaa 180
gacctcaac aacaagtttg cctcctcat cgacaagggt cggtttcttg agcagcagaa 240
caagctgctg gagaccaagt ggacgtgct gcaggagcag aagtcggcca agagcagccg 300
cctcccagac atctttgagg ccagattgc tggccttcgg ggtcagcttg aggcactgca 360
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caagaataag tacgaagatg aaattaaccg ccgcacagct gctgagaatg agtttgtggt 480
gctgaagaag gatgtggatg ctgcctacat gagcaagggt gagctggagg ccaagggtga 540
tgccctgaat gatgagatca acttcctcag gacctcaat gagacggagt tgacagagct 600
gcagtcccag atctccgaca catctgtggt gctgtccatg gacaacagtc gctccctgga 660
cctggacggc atcatcgctg aggtcaaggc rcagtatgag gagatggcca aatgcagccg 720
ggctgaggct gaagcctggt accagaccaa gtttgagacc ctccaggccc aggctgggaa 780
gcatggggac gacctccgga ataccggaa tgagatttca gagatgaacc gggccatcca 840
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tgccgaggct gaggagcgtg gggagctggc gctcaaggat gtcgtgcca agcaggagga 960
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ggagggcgag gagagccggt tggctggaga tggagtggga gccgtgaata tctctgtgat 1140
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gggcagcaat gccctgagct tctccagcag tgcgggtcct gggctcctga aggttattc 1260
catccggacc gcatccgcca gtcgcaggag tgcccgcgac tgagccgcct cccaccactc 1320
```

cactcctcca gccaccaccc acaatcacaa gaagattccc acccctgcct cccatgcctg 1380
 gtcccaagac agtgagacag tctggaaagt gatgtcagaa tagcttccaa taaagcagcs 1440
 tcattctgag gcctgagtga aaaaaaaaaa aaaaanaaaa aaaaaaattt tngggggggg 1499

<210> 46
 <211> 393
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (167)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (178)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (219)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (359)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (372)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (378)
 <223> n equals a,t,g, or c

<400> 46
 tcgacccacg cgtccggcag cctttctgag ggagcggttg tgtgttcgcc atcttaggaa 60
 gaagatgttc tcgtccgtgg cgcattctggc cgggcgaacc ccttcaacgc gccccacctg 120
 cagctggtag acgatggcct caccgggcacc gaagcagccc cgtgggnacc cccgggcncg 180
 ccccgaaagt tcccgaatc tggcagcagc cgctgtggna agagtacagt tgccaatatg 240
 gctccatgaa gttttatgca ctgtgtggct ttgggtgggt cttagttgt ggtctgacac 300
 aactgtctgt cgttctctg gatttagtga aatgccgaat gcargtgga cccagaant 360
 acaagggcak wnttaatngg attctcatta aca 393

<210> 47
 <211> 238
 <212> DNA

<213> Homo sapiens

<400> 47

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cggatcccg ctcctgcac cagtcgccat tcgggaggcc gctgcgctgc agggcctcgc 60
ggaccgccc cgaccgcgag ccgggccctc cgcgcggtcc atcgcccact ggacgccgcc 120
cgcggccgga ccggttcaac ttctcatctt tgttcttctt catatactat aggtgtttg 180
ctgtggttta gtcaaaaagc catgtagaat gcctgccttt tgaagaccac ttttaagg 238
```

<210> 48

<211> 939

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (937)

<223> n equals a,t,g, or c

<400> 48

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gccaccatct tggaacggga ggcgagcag agtcgactgg gagcgaccga gcgggccgcc 60
gccgccgcca tgaaccccga atatgactac ctgtttaagc tgcttttgat tggcgactca 120
ggcgtgggca agtcatgcct gtcctgcgg tttgctgatg acacgtacac agagagctac 180
atcagacca tcggggtgga cttcaagatc cgaaccatcg agctggatgg caaaactatc 240
aaacttcaga tctgggacac agcgggccag gaacggttcc ggaccatcac ttccagctac 300
taccgggggg ctcattggcat catcgtggtg tatgacgtca ctgaccagga atcctacgcc 360
aacgtgaagc agtggctgca ggagattgac cgctatgccg gcgagaacgt caataagctc 420
ctggtgggca acaagagcga cctcaccacc aagaagggtg tggacaacac cacagccaag 480
gagtttgtag actctctggg catcccttc tggagacga gcgccaagaa tggcaccaat 540
gtcagcagg cgttcatgac catggctgct gaaatcaaaa agcggatggg gcctggagca 600
gcctctgggg gcgagcggcc caatctcaag atcgacagca cccctgtaa gccggctggc 660
ggtggctgtt gctagsagg gcacatggag tgggacagga gggggcacct tctccagatg 720
atgtccctgg agggggcagg aggtacctcc ctctccctct cctggggcat ttgagtctgt 780
ggctttgggg tgtcctgggc tcccattctc ctctggccc atctgcctgc tgccctgagc 840
cccggttctk tmagggtccc taaaggagga cactcagggc ctgtggcagg caggggcgag 900
gctgcttggt ctgttgctc taagtgaatt tccaaangc 939
```

<210> 49

<211> 1771

<212> DNA

<213> Homo sapiens

<400> 49

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tttgagagc actccaacca gctgtggaac atcagcgccg tcccttctctg gtccaaagt 120
aaccagggtc tcatccgcat gtataaggcc gagtgcctgg agaagtccc tgtgatccag 180
cacttcaagt tcgggagcct gctgccatc catcctgtca cgtcgggcta ggaggggcca 240
agccgaagag ccaccaggc cacagttcct gtgcctgcct tccccacccc agcagtggcc 300
cctccccatc ccctccctct gtctgtcccg tttgatgaga ggctgtttac tggggtgggg 360
tggcgagatg ggcttgaggg ggctcagagc ataaggcttc agggcccaag ttgggagaag 420
tgaccaaagt gtagccagtt ttctgagttc ccgtgtgcta gactggccag aagagaggg 480
ctggggccctg gtcactcggc cactctctcc tgtttctggc ctcttctccc ttcactcccc 540
```

```

tccagtctgg ttttgagagc aggggctgtt ctgcagcacc kcagggaagg gaggagagat 600
acctgctgct tccattgctt ttcccttcct ggagtcgatg cctttctaag ggttgagact 660
gctccttgca ggggcgggtc agtttcccag gccatgccgg ggtggccatc tatgctaggg 720
ctggaagctg aggttgcccg ccagctgtgg gctggggtgg ggtgggtggg gtcgggtggg 780
ggagaggcct tagctgtcct ggctggtgcc cctcccaggc tccttttcac cctgccccct 840
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caaaggtcag tgacagtttc tcagaagagg ccagcgtcc acctctctcc cagggccaga 1620
cacccttcc tggtccccc atccccctat ggctcccagc cccttgacc ctcatgtctg 1680
ttcagattaa agcctctgtt ttgcacctgt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1740
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```

<210> 50

<211> 397

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (201)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (207)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (352)

<223> n equals a,t,g, or c

<400> 50

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gggtcgaccc acgcgtccgc tcgctccggg atcgcccgcg ctagagacgc atagcgtctt 60
aatcgctcgc acgcaccggc cctcgctcgc tcgcccgtcc gtgcccgcgc cgccagccc 120
accgccaccc tttgcagcca tgtccaccag gtcygtgtcc tcgtcytcct accgcagatg 180
ttcgcgccgc ccggcaccgg naggcgnccg agctccacgc gcataacgtg accagtccac 240
ccgcacctac agcctgggca gcgcctgcgc cccagcacca gccgcagcct ctamamctcg 300
tccccgggag gcgcgtatgt tcacggctcc ttccgcggtg cgcctgcgga anatgttgcc 360
ccggcggtgc gcttgctggc aggattccgt ggaattt 397

```

<210> 51
<211> 1635
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1422)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1617)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1620)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1629)
<223> n equals a,t,g, or c

<400> 51
gccacgcgt cgcgccacgc gtccgcccac gcgtccgcct ctccagccct tctcctgtgt 60
gcctgcctcc tgccgcgcgc accatgacca cctccatccg ccagttcacc tcctccagct 120
ccatcaaggc ctcctccggc ctggggggcg gctcgcccg caccctcctgc cggctgtctg 180
gcggcctggg tgccggctcc tgccagctgg gatctgctgg cggcctgggc agcaccctcg 240
ggggtagcag ctactccagc tgctacagct ttggctctgg tgggtggctat ggcagcagct 300
ttgggggtgt tgatgggctg ctggctggag gtgagaaggc caccatgcag aacctcaatg 360
accgcctggc ctcctacctg gacaaggctg gtgccctgga ggaggccaac actgagctgg 420
aggtgaagat ccgtgactgg taccagaggc agggcccggg gcccgcctg gactacagcc 480
agtactacag gacaattgag gagctgcaga acaagatcct cacagccacc gtggacaatg 540
ccaacatcct gctacagatt gacaatgcc gtctggctgc tgatgacttc cgcaccaagt 600
ttgagacaga gcaggccctg cgcctgagtg tggaggccga catcaatggc ctgcgcaggg 660
tgctggatga gctgaccctg gccagagccg acctggagat gcagattgag aacctcaagg 720
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tgggtgggtga gatcaatgtg gagatggacg ctgcccagg cgtggacctg agccgcaccc 840
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cccacctgac tcagtacaag aaagaaccgg tgaccaccg tcagggtgcgt accattgtgg 1320
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gaggactcag ctaccccgcc cggccaccca ggaggcagg angcagccgc cccatctgcc 1440
ccacagtctc cggcctctcc agcctcagcc ccctgcttca gtcccttccc catgcttctc 1500

```
tgcctgatga caataaagct tgttgactca gctaaaaaaa aaaaaaaaaa aaaaaaaaaa 1560
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaanttn 1620
gggggggggnc ccccc 1635
```

<210> 52

<211> 1780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1780)

<223> n equals a,t,g, or c

<400> 52

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ccgccgccgc cgccgccgcc ggagctctgt agtatggcat cgaggagaat ggagaccaa 60
cctgtgataa cctgtctcaa aaccctcctc atcatctact ccttcgtctt ctggatcact 120
ggggtgatcc tgctggctgt tggagtctgg ggcaaaactta ctctgggcac ctatatctcc 180
cttattgccg agaactccac aaatgtctcc tatgtgctca tcggaactgg caccactatt 240
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ctgtatgcca tgtttctgtc cctgggtgtc ctggctgagc tcgtagctgg catttcaggg 360
tttgtgtttc gtcattgat caaggacacc ttcctgagga cttacacgga cgctatgcag 420
acttacaatg gcaatgatga gaggagccgg gcagtggacc atgtgcagcg casctgagct 480
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tcccccccag ctgctgcatg aacgaaactg attgtaatcc ccaggatcta cacaatctga 600
ctgtggccgc caccaaagtt aaccagaagg gttgttatga tctggtaact agtttcatgg 660
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gcatgctgct ggccgtgctg ctgtcccggg tcacacgggc caatcagtat gagatggtgt 780
aaggagaagt ctttcaagaa tgacggaata agagacctgt tttaaaaagg aactgcagca 840
atctttgaaa gacttccaaa gaatgttaga gcacagtaca taatacactt gccctgctcc 900
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ttcttgatga ggccatgata ttttggtttt ccccaattaa ttgctattgt gttattttac 1560
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aatttaaaaa tgagtgtgaa gggggaacaa gtcaaaatat ttttaaaaga tcttcaaaaa 1680
taatgcctct gtctagcatg ccaacaagaa tgcattgata ttgtgaacat ttgtgatata 1740
tgtattaata aatagagcaa ttacaagcaa aaaaaaatgn 1780
```

<210> 53

<211> 490

<212> DNA

<213> Homo sapiens

<400> 53
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aggcaggaga ataccctcc ctaagccctt agtgtgtgcc gagcttgctt tgtgatgtg 180
gcaggggagg ggagacctgg gtggtgactg agttcccttt atcaaaccct tcaatgggca 240
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catttctgga gcagggcctg agaccctgcc acatctccta tgctctgcat ccacgcctct 420
tttgacatt aaaggttgat tgatgcaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480
aaaaaaaaa 490

<210> 54
<211> 1944
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (466)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (634)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1308)
<223> n equals a,t,g, or c

<400> 54
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ctgggcagtg ttggccgctg gcggagcgtt ggggcagcat gaagtgcctg gtcacgggag 120
gcaacgtgaa ggtgctcggc aaggccgtcc actccctgtc ccgcacggg gacgagctct 180
acctggaacc cttggaggac gggctctccc tccggacggt gaactcctcc cgctctgcct 240
atgcctgctt tctctttgcc ccgctcttct tccagcaata ccaggcagcc acccctgggt 300
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cgatgctgga gaagacggtg gaaaaatgct gcatctccct gaatggccgg arcagccgcc 420
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ctgtgagtcc ctgcaggccg tcttcgaccc agcctcgtgc cccacatgc tccgcgcccc 540
agcacgggtt ctgggggarg ctgttctgcc cttctctcct gactgggtg aagtgcgct 600
gggcattggc cgtggcgag gktcatcctg gcantaccac gaggaggagg cagacagcac 660
tgccaaagcc atggtgactg agatgtgcct tggagaggag gattccagc agctgcaggc 720
ccaggaaagg gtggccatca ctttctgcct caaggaattc cgggggctcc tgagctttgc 780
agagtcagca aactgaatc ttagcattca ttttgatgct ccaggcagge ccgccatctt 840
caccatcaag gactctttgc tggacggcca ctttgtcttg gccacactct cagacaccga 900
ctgcgactcc caggacctgg gctcccaga gcgtcaccag ccagtgcctc agctccaggc 960
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tggccccag ccccccaaga gccccggtcc ccactccgag gaggaagatg aggetgagcc 1140

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cagtacagtg cctgggactc cccaccccaa gaagttccgc tcactgttct tcggtccat 1200
cctggcccct gtacgtcccc cccagggccc cagcctgtgc tggcggaaga cagtgaggg 1260
gaaggctgaa ccaagaacct gaagcctgta cccagaggcc ttggactnag acgaagcccc 1320
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tggccctgaa ctactgacgt tcctacctct tatttctcat tgagcctcag gctatactcc 1560
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tgccctggct ggggcccggg gccgagactc ccaagcggst ctgtgcagaa gagctgccag 1860
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gagaccagat gggtttgccc cagg

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<210> 55

<211> 994

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (896)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (971)

<223> n equals a,t,g, or c

<400> 55

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gaaggtagcg accgtcgccg gcagcgccgc gaaggcgtgc tcgggccagc ccttctctgc 180
cgccctggg aggttctagg cgcacacgag gtcccctcga ggaacatctt ttcagaacaa 240
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ggcatcgggc cagagctcat gctgcatgtc aagtcctgtc tcaggcacgc atgtgtacca 360
gtggactttg aagaggtgca cgtgagttcc aatgctgatg aagaggacat tcgcaatgcc 420
atcatggcca tccgccggaa ccgcgtggcc ctgaagggca acatcgaaac caaccataac 480
ctgccaccgt cgcacaaatc tcgaaacaac atccttcgca ccagcctgga cctctatgcc 540
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ctcattgtcc gggagaacac agaggcgag tacagcagcc tggagcatga gagtgtggcg 660
ggagtgggtg agagcctgaa gatcatcacc aaggccaagt ccctgcgcgt tgccgagtat 720
gccttcaagc tggcgagga gagcgggcgc aagaaagtga cggccgtgca caaggccaac 780
atcatgaaac tgggcgatgg gcttttcctc cagtgtgca gggagggtgc agccggttac 840
cctcagwtca ccttcgagaa catgattgtg gataacacca ccatgcagct ggtgtnccgg 900
ccccagcagt ttgatgtcat ggtgatgcc aatctctatg gcaacatcgt caaacaatgt 960
ctgcgcggga ntggtcgggg gcccaagctt gttg

```

<210> 56

<211> 328

<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (123)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (156)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (170)
<223> n equals a,t,g, or c

<400> 56
gggtcgaccc acgcgtccgc ccacgcgtcc ggatgacttc attgccaaag ttgttcaaag 60
gtagccttgg ccctttttca tctgagtcgc atttagagat gtataaagaa tgttgttgag 120
tanggcgcgg tggtcacgc ctgtaatccc cacacnttgg gaaggccgan gcaggcggat 180
cacgaggtca gaagattgag accattctgg ctaacatggt gaacccccat ctctactaaa 240
aatacaaaaa ttagtcaggc gcgatggcgg gcacatgtag taccagctac tcgggagggt 300
gatgcagaag aataacttgg aacctggg 328

<210> 57
<211> 1489
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (710)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1109)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1117)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1206)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1211)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1218)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1264)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1311)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1446)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1467)
<223> n equals a,t,g, or c

<400> 57
cggcacgagg ggtggtgtgg gtgtgttttag aaaaaagatg cattcctgaa gatctctggt 60
gctgaagggc ctcgagttcc tttcagagac tgtatttgac acacttttagg tacacacaaa 120
cgaatggtat cacatgcaat attttaatgg agcaatggga gaggctcttt gaaatggggg 180
ttgcatcttt ttgtaacatt ttgattttctc tgggtgcctta ttctacttg atgctggcac 240
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tgtttgagca tgcagggggc atggggagtt tgggtgtcagt tgggtggagaa gggactagat 360
ggcatctctt agccgaggcc aacaggaact gcacaagtcc attatagtca aagttagcaa 420
ttttgatacg taaacacaat acttcattct tcctcatctg agctttcctt ccttcttctc 480
tttctatctc taccttctca taaagggtgct gctgctgctg ctaagggtgcc cggagtccag 540
aatgtccatt aatcactcag gcacgagcct ggcactgcca cgtcagcccc cagcatgacc 600
aaaccacagg ttctcttgct tggggctgag aactgtcaga tttttctcat caaaaatggt 660
ttccaaggaa tcagtggatt acagtttttc tgcattgaaa atgcactttn aaaaaataaa 720
ttaagctcc agactgttta aaatatacag agggagcagg ggaaagttaa gcatgtgcta 780
gtgtctgaac ccagttcagt ttatctccag ttgaaacgat atacactata ttatgtataa 840
atgtatacac acttctata tgtatccaca tatatatagt gtatatatta tacatgtata 900
ggtgtgtata tgtgcatata tacacacatg cacataacaa aatcagatgc tcattacaaa 960
tccagatgct cattacaaaa ccagatgcta cacaaacagc agcagaggaa acaagggttg 1020
actcttgcaa cagatcacia aaaataaaaa cagctacttg cagtgaactt ggtcatttct 1080
gtatgttcat aaagaatgga tttgtaacna ggaaaaanaag gaccagtgtt agtgaaaagg 1140
gaagatgggg cgaaccatct tgatccgatg cgaatccgta atgggtctata tacatttcat 1200

```

cagtantcat ntagtcangt gattgattca gttctgctat gaaacattgt aacacgtacc 1260
cacnactgac aactactcgt gagcgttcat taggagtgac ctaactttgc ntgcctgctc 1320
atgggacgag ctcccttaggt ggagataccg gggaaatagag aaagatgcac gtctctgcgt 1380
tgctcgctgc tttgaggggc ggtctttacc ttccgtgttg gagtcctccc tgagtcgggc 1440
gctggntgcg ggacacggcc cttctcngtg tcccaggcgc tgcctcatt 1489

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<210> 58

<211> 1283

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (38)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (550)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1242)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1250)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1260)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1263)

<223> n equals a,t,g, or c

<400> 58

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aggtaatttg aattgagaga gagtaagtga cttgctgnaa aaaggggtaa tcaacagcag 60
agctgggatt tgaaccata actctgtcaa agcctccact cctaactcct gttcatgctc 120
ctgtggagaa aatgcttgta gtaacatatt ttaaattgtac taacaagacc agtcatgggm 180
aaatgtttct gagacaaatc tctagtttat gatttaaaac agtacgtttt cttacgtgac 240
gaaaacaaaa agtgtgttaa tttgttccca gtggttgaag ttatttgcca acaattttac 300
tgtttctctt catctgttta taggatttct ctgcctcttc caaacttttc ctccctgaac 360
ctgaggggta agcattttat ttcccttttag gaaaaacgac agctgcttgt aaccactgtg 420
tttatgtcaa agcattcatt ttttttagga tatctgaaaa aatgccatat aagaraaaam 480
tctataaaac atctatwatt ttcgaacca agtacactct tgcattctaw gctttaagtt 540

```

```

aaatgcaaan tcctttttcc ttcttcctgc tgcaagtact atctcatcct gatgctcaag 600
agtgtcaggg cctgggtttc caaacagaga ctaccctaaa attatttggc gagtagtact 660
ttacacaatt gcctctcccc cacaaatcat aattgtttca gtaaaatggg tacttggttt 720
ttccaagaaa aaactcgttt ttactcattt ttggcctggt tgtttattta gaaactaatc 780
tggtattcact ccctctggtt gataccctact caaaaaggac acttctgatt aagacgggtg 840
aaactagaga tggacaggtt atcaacgaaa cttctcagca tcacgatgac cttgaataaa 900
aattgcacac actcagtgcg gcaatatatt accagcaaga ataaaaaaga aatccatata 960
ttaagaaaac agctttcaag tgcttttctg cagtttttca ggagcgcaag atagatttgg 1020
aataggaata agctctagtt cttaacaacc gacactccta caagatttag aaaaaagttt 1080
acaacataat ctagtttaca gaaaaatctt gtgctagaat acttttttaa aggtattttg 1140
aataccatta aaactgcttt tttttttcca gcaagtatcc aaccaacttg gttctgcttc 1200
aataaatctt tggaaaaact maaaaaaaam mngggggggg gcccggggtn 1260
ccnccggggg gcccaagttt tac 1283

```

<210> 59

<211> 740

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (696)

<223> n equals a,t,g, or c

<400> 59

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agaaggagcg cggggaggac gtaccttgtg agatgcgagc cggccaacag cttgcaagca 60
tgctccgctg gacccgagcc tggaggctcc cgcgtgaggg actcggcccc cacggcccta 120
gcttcgcgag ggtgcctgtc gcacccagca gcagcagcgg cggccgaggg ggcgccgagc 180
cgaggccgct tccgctttcc tacaggcttc tggacgggga ggcagccctc ccggccgctc 240
cttttttgca cgggctcttc ggcagcaaaa ctaacttcaa ctccatcgcc aagatcttgg 300
cccagcagac aggccgtagg tgctgacggt ggatgctcgt aaccacggtg acagccccc 360
cagcccagac atgagctacg agatcatgag ccaggacctg caggaccttc tgccccagct 420
gggcctggtg ccctgcgtcg tcgttgcca cagcatggga ggaaagacag ccatgctgct 480
ggcactacag aggccagagc tgggtggaac tctcattgct gtagatatca gccagtgga 540
aagcacaggt gtctcccact ttgcaacctt tgtggcagcc atgagggcca tcaacatcgc 600
agataggctt gcccgcctcc cgtgcccga aactggcgga tgaacagctc agttctgtca 660
tccaggacat ggccgtgcgg cacacttgct tcaatnaacc tggtagaggt agacgggcgt 720
tttcgtgttg gaggtgga 740

```

<210> 60

<211> 1291

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (7)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (147)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1211)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1283)

<223> n equals a,t,g, or c

<400> 60

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ttaggtacaa agcctcgctc tttgtcccca tctgtcgttc acacgaactc aagccttttg 120
cattcggcag ccaatagaat ctaaganatg gcggaaaaat gattccgcct cgggagctaa 180
acttgattgg cagtttagct aaccaatcga gaacgccatt tgtamccctt ggcaggcamc 240
gagctccgtc gtctcgtttc cggcggtcgc gcgctctttt ctggggacgg gagaggccgt 300
gtagcgtcgc cgttactccg aggagatacc agtcggtaga ggagaagtcg aggttagagg 360
gaactgggag gcactttgct gtctgcaatc gaagttgagg gtgcaaaaat gcagagtaat 420
aaaactttta acttgagaa gcaaaaccat actccaagaa agcatcatca acatcaccac 480
cagcagcagc accaccagca gcaacagcag cagccgccac caccgccaat acctgcaaat 540
gggcaacagg ccagcagcca aaatgaaggc ttgactattg acctgaagaa ttttagaaaa 600
ccaggagaga agaccttcac ccaacgaagc cgtctttttg tgggaaatct tcctcccgac 660
atcactgagg aagaaatgag gaaactatct gagaaatatg gaaaggcagg cgaagtcttc 720
attcataagg ataaaggatt tggctttatc cgcttggaac cccgaaccct agcggagatt 780
gccaaagtgg agctggacaa tatgccactc cgtggaaagc agctgcgtgt gcgctttgcc 840
tgccatagtg catcccttac agttcgaaac ctctctcagt atgtgtccaa cgaactgctg 900
gaagaagcct tttctgtgtt tggccaggta gagagggctg tagtcattgt ggatgatcga 960
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gagcccatgg accagttaga tgatgaagag ggacttccag agaagctggg tataaaaaac 1140
cagcaatttc acaaggaacg agagcagcca cccagatttg cacagcctgg ctcccttkga 1200
gtatgaatat ngccatgcgc tgggaaggca ctcatgaga tggagaaagc agcctggggg 1260
gacaagaagt gaagactcct gntccaaaa a 1291
```

<210> 61

<211> 971

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (856)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (886)

<223> n equals a,t,g, or c

<400> 61

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ctgcagtacc ggtccggaat tcccgggtcg acccacgcgt ccgggtctgt ggtcctctct 60
cggctcctcg cggctcgcgg cgcccgacgg ttccctgggac acctgcttgc ttggcccgtc 120
cggcggtcga gggcttctct gctgcgctcc cggttcgctg gacgggaaga agggctgggc 180
cgtcccgctcc cgtcccatc ggaaccccaa gtgcgcgcgc tgaccgctcg cagggcgaga 240
tgagcgcgga cgcagcggcc ggggcgcccc tgccccggct ctgctgcctg gagaagggtc 300
cgaacggcta cggcttcac ctgcacgggg agaaggga gttgggccag tacatccggc 360
tggtggaacc cggctcgcc gccgagaagg cggggctgct ggccggggac cggctggtgg 420
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agccgcccgc cgccgccrag gtgcaggggg ctggcaacga aaatrarcct cgcraggccg 660
acaagagcca cccggagcag cgcgagcttc ggcctcggct ctgtaccatg aagaagggcc 720
ccagtggcta tggcttcaac ctgcacagcg acaagtcaa gccaggccag ttcacccggt 780
cagtggaccc agactccccg gctgaggctt cagggtccg ggcccaggat cgcattgtgg 840
aggtgatgct tctcgnctct ctccctatct gaactgcccc caaccnctgc agattagcag 900
caccttgggg cagccatcat accatcatgg ggtttgatta gcccacgggc attagccaac 960
ctgggaggtt g                                     971

```

<210> 62

<211> 618

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (563)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (598)

<223> n equals a,t,g, or c

<400> 62

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ggaccacgc tgcattttca tcgaaagagt gaacatctag tgggactgaa agttctttgt 120
tgtttcagat tgtagagtgt gattgatgga attggtctgt ggaattgca ttgtttttat 180
ttctttatgt aatcagttta agtaataggg ggtatatata atcgtaagta ttttaggggtg 240
ggaggggcta ttaagtaatt aagtgggtgg ggttagttta aaagttagca tgatatgtat 300
tagataactc tataagtga catgtgtact tacttgtgat cctttaccct atgattgcta 360
cccttaacga ttcaaataa actcagaggg aactgcaggg agatcaaacc atttagggca 420
aattggacat gaataaaact ctagtgggaa aaagttcaaa ggtgattgaa taaataattt 480
aactttgccc tgggtattaa gtccagggct cccagattgt ggagcagagc cttggagagt 540
acaggatgaa ggagatagat gcncctttga cttgccggga atgaaattgg attaatgnaa 600

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ggatggtaaaa taattcca

618

<210> 63

<211> 1138

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (7)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (15)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (22)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (27)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (29)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1123)

<223> n equals a,t,g, or c

<400> 63

tctatanatc atganaggaa anggtancng acagtacggt cggattcccc ggtcgacca 60
 cgctccgatg acttcacccc tctggagatc ctctggacct tctccatcta cctggagtca 120
 gtggccatct tgccgcagct gttcatggtg agcaagaccg gcgaggcgga gaccatcacc 180
 agccactact tgtttgcgct aggcgtttac cgcacgctct atctctcaa ctggatctgg 240
 cgctaccatt tcgagggtct cttcgacctc atcgccattg tggcaggcct ggtccagaca 300
 gtcctctact gcgatttctt ctacctctat atcaccaaag tcctaaaggg gaagaagttg 360
 agtttgccgg catagccccg gtcctctcca tctctctcct cggcagcagc gggaggcaga 420
 ggaaggcggc agaagatgaa gagctttccc atccaggggt gactttttta agaaccacc 480
 tcttgtgctc cccatccccg ctctgcccgg gtttcagggg gacagtggag gatccaggtc 540
 ttggggagct caggacttgg gctgtttgta gttttttgcc ttttagacaa gaaaaaaaaa 600
 tctttccact ctttagtttt tgattctgat gactcgtttt tcttctactc tgtggcccca 660
 atttttataa agtggttttg agtgcctat gggccggggc agggccaag atcttttccc 720
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ctaaatctgc cgacacccat ctgccccacc tcctgccatg gccatgaacc gcgaccccca 840
ctaaatttct agattgggga tagggagaaa gggaggccca ggaaggtctc ccctgatttt 900
tttcatagtg aatttttttc cccagagttt gaattttttg gtcttctcct ggttttttgg 960
caaattaggg gggcccgagg ctcaagtgcg ggaagggggc tggcccgagg atcccatggc 1020
tctcacacca tgtttttgta cagaactgat ggttgaatct ttgttctctt gaaataaaca 1080
gaagaaaatg aaaccttaaa aaaaaaaaaa aaaaaaaaaa acncgggggg gggcccgagg 1138

<210> 64

<211> 418

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (365)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (371)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (380)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (391)

<223> n equals a,t,g, or c

<400> 64

tgctcatcca gaggagctca ccacagtcac tgcgacagac tgccacactc accctggcct 60
ggcctcagag aagttgagct actggcctca gtacacacag agcagatgga ggaagagctg 120
gcactaggac ccagggggca ggggggagcc tccctggctg gaagggatgg caggagcgct 180
ggtgcaggta gctatggagc tctggccaac tctgcctggg gaggtcccag gaagggtggc 240
tcagcatctg cagccgcgtc gacgttgctg gagcctccgc ggaggaccca ggagagccgg 300
actaggacca gggccctggg cctccccaca ctccccatgg agaagctggc ggcctctaac 360
agagncccaa ngggcttggn cggctcctggg ncgtgaaaat gttcaagtgc ccgattga 418

<210> 65

<211> 2836

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2834)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2836)

<223> n equals a,t,g, or c

<400> 65

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aagaaaccgc ccattacaca cccaggtaca ccagcagagg aaacttataa cctcgggagg 60
caggtccttc ccctcagtgc ggtcacatac ttccagaaga gcggaccagg gctgctgcc 120
gcacctgcca ctcagagcgc ctctgtcgct gggacccttc agaactctct ttgctcaca 180
gttaccaaaa aaaaaagagc caacatgttg gtattgctgg ctggtatctt tgtggtccac 240
atcgctactg ttattatgct atttgttagc accattgcc  atgtctggtt ggtttccaat 300
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ccctcattaa agcngn                                     2836

```

<210> 66

<211> 2305

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1973)

<223> n equals a,t,g, or c

<400> 66

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cgggagcctg tcccgtagct ttagg 2305
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<210> 67
<211> 1907
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1221)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1655)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1896)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1904)
<223> n equals a,t,g, or c

<400> 67
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cgggcaagac ccattagggc gagatcgtgg aaggggagaa ccacacctac tgcattccgt 180
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<210> 68

<211> 815

<212> DNA

<213> Homo sapiens

<400> 68

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tgatacacia ctgctatttt taatttagaa ctttgacctt atttgggttt tcaaaacccat 720
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<210> 69

<211> 1150

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (14)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (23)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (25)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1150)

<223> n equals a,t,g, or c

<400> 69

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aaaaaaaaaa aaaaaaaaaa aaaaaaaraa aaaaaaaaaa aaaraaaraa aaaaaawaa 1140
gaaaaaaaaa                                     1150

```

<210> 70

<211> 344

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (287)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (333)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (339)

<223> n equals a,t,g, or c

<400> 70

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caaagtctat tctccagttg ccagagtcag agctgggtga atactctctg gggggctaca 180
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agctgattga tctgatatac tgtggccgga agcttaaaga tgaccanacc ttgacttcta 300
cggatttcaa cctgggtcca catccatgtt ctncggaant cctg 344
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<210> 71

<211> 448

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (425)

<223> n equals a,t,g, or c

<400> 71

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gcaggagaga atttcgataa attggtgtct ggaaagtga gagaaatttt gaacatatct 240
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agcgtggtgg tggtcggcct cggcagaaaag gcagctggag tcgatgacca ggaaaactgg 360
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<210> 72

<211> 2825

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1809)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2093)

<223> n equals a,t,g, or c

<400> 72

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gcagctgtca atgacactcc gaggtggccg aggcataagac aagaccaatg gtgcccctga 180
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ctcggatgag gtgcagtctc cagtgaagat gcgtatgcgc aaccatcccc cagcaagat 420
ctccactgag gacatcaaca agcgcctatc actaccagct gacatccggc tgcctgaggg 480
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aaaaa 2825

<210> 73

<211> 510

<212> DNA

<213> Homo sapiens

<400> 73

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atgtacgaga gcgcacccaa agaacctagt agagaaaggt attctaacca ctgagaagca 60
gaatttccts ctatttgaca tgactactca tccagtgacc aatacaacag agaaacagcg 120
actagtgaag aaacttcaag atagtgtact agagcgggtg gtaaatgacc ctgagcgat 180
ggacaagcga acactagcac tcctgggtgct agcccactcc tctgatgtgc tagagaatgt 240
cttctcctct ctgacagatg acaagtatga tgtggcaatg aatcgagcca aggacttagt 300
agaactggac cctgaagtgg aagggacaaa gccyagtgcc acagaratga tctgggctgt 360
gctggcagcc tttyaataaa tcytaaagcc rgyrggtggg tttctycttt tcccctgctg 420
gctggtgact gttcagagac mccwactga gttttgtgtg atgasatgtt ttccatcatt 480
ttttccttyc ttgaatcaga cttgtgaatt 510

```

<210> 74

<211> 458

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (382)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (388)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (424)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (448)

<223> n equals a,t,g, or c

<400> 74

```

gggtcgaccc acgcgtccgc tccacttaaa attcaacttc tgcttggttc atctgattct 60
ttcaagggtct taaatgttaa atgaaggggt aaaataggaa ggtatttaag taattagcag 120
gcctcctggg tcttgataac ttcagtgtct ctgggagctg cccggttggc caccagtctc 180
tgtggaatcc aggggcctct tcccaatatg gatttgacca gcacttcaat tagtgagttt 240
ccatkagcat cttagcatta ctctttaata cagacgcctt attttccagg gtttatgaaa 300
gtttaagtga caaccatgga ttgcaggaac agactgttga gaagctgttt ttccagtgga 360
aaagttgggt ccaggagatg angggagnct tgaaatagat cctgggatgg aaacataaag 420
tgngcagcca gattcccatc atgggctncc ccataaaa 458

```

<210> 75

<211> 377

<212> DNA

<213> Homo sapiens

<400> 75

```

gtcctggaaa cacatcaagc tcagctcctg tgtccagctc gcttctctgc tggactcctt 60
gatttttttt ttaatcattg tttgattttg agcagtaacc aggctttttt ttccagatgt 120
tagtccacac ctattcatcc atggaccggc acgatgggtg. cccgagccac agctcgcggc 180
tctcccagct gggtcgggtg tcccaaggac cctactcgag cgccccgccg ctgtcccaca 240
ccccgtcgtc ggacttccag cgcgcctact tcccamcccc ctaccagccg ctccccctamc 300
amcagagcca ggacccctac tcccacgtca amgameccta tccctgaacc cactgcacca 360
gccccagcaa catccct                                     377

```

<210> 76

<211> 2070

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (39)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (88)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2068)

<223> n equals a,t,g, or c

<400> 76

```

tcatgaatgg gaatcctggn cccaagaact ccgcttgcng ccagagggac ctgcagctga 60
ggacctatag cgttgtgccc atgacctnca gtgtatocca gggcaccgcc gtgtgtaata 120
taaagattgg ctgacaaaaa tgtcaggaaa acatgatgtt ggagcttaca tgctaata 180
taagggcgct aatcgtactg aaacagtcac gtcttttaga aaacgagaaa gttaaagtcc 240
tgctgatctc ttaaagcggg ccttcgtgag gatgagtaca agccctgagg ctttcctggc 300
gctccgctcc cacttcgcca gctctcacgc tctgatatgc atcagccact ggatcctcgg 360
gattggagac agacatctga acaactttat ggtggccatg gagactggcg gcgtgatcgg 420
gatcgacttt gggcatgcgt ttggatccgc tacacagttt ctgccagtcc ctgagttgat 480
gccttttcgg ctaactcgcc agtttatcaa tctgatgtta ccaatgaaag aaacgggcct 540
tatgtacagc atcatggtac acgcactccg ggccttccgc tcagaccctg gcctgctcac 600
caacaccatg gatgtgtttg tcaaggagcc ctcttttgat tggaaaaatt ttgaacagaa 660
aatgtgaaa aaaggagggt catggattca agaataaat gttgctgaaa aaaattggta 720
ccccgcagac aaaatatgtt acgctaagag aaagttagca ggtgccaatc cagcagtcac 780
tacttgtgat gagctactcc tgggtcatga gaaggcccct gccttcagag actatgtggc 840
tgtggcacga ggaagcaaag atcacaacat tcgtgcccaa gaaccagaga gtgggctttc 900
agaagagact caagtgaagt gcctgatgga ccaggcaaca gacccaaca tccttggcag 960
aacctgggaa ggatgggagc cctggatgtg aggtctgtgg gagtctgcag atagaaagca 1020

```

```
ttacattggt taaagaatct actatacttt ggttggcagc attccatgag ctgattttcc 1080
tgaaacacta aagagaaatg tcttttgtgc tacagtttcg tagcatgagt ttaaatcaag 1140
attatgatga gtaaatgtgt atgggttaaa tcaaagataa gggtatagta acatcaaaga 1200
ttaggtgagg tttatagaaa gatagatata caggcttacc aaagtattaa gtcaagaata 1260
taatatgtga tcagctttca aagcatttac aagtgtctga agttagtga acagctgtct 1320
ccgtaaattg aggaaatgtg gggaaagcctt ggaatgccct tctgggtctg gcacattgga 1380
aagcacactc agaaggcttc atcaccaaga ttttgggaga gtaaagctaa gtatagttag 1440
tgtaacattg tagaagcagc ataggaacaa taagaacaat aggtaaagct ataattatgg 1500
cttatattta gaaatgactg catttgatat tttaggatat ttttctaggt tttttccttt 1560
cattttattc tcttctagtt ttgacatttt atgatagatt tgctctctag aaggaaacgt 1620
ctttatttag gagggcaaaa attttgggtc tagcattcac ttttgctatt ccaatctaca 1680
actggaagat acataaaaagt gctttgcatt gaatttggga taacttcaaa aatcccatgg 1740
ttgttgtagg ggatagtact aagcatttca gttccaggag aataaaagaa attcctatct 1800
gaaatgaatt cctcatttgg aggaaaaaaa gcattgcatt tagcacaaca agatgaaatt 1860
atggaataca aaagtggctc cttcccatgt gcagtccctg tcccccccg ccagtcctcc 1920
acacccaaac tgtttctgat tggcttttag ctttttgttg tttttttttt tccttctaac 1980
acttgatatt ggaggctctt ctgtgatttt gagaagtata ctcttgagtg ttttaataag 2040
tttttttcca aaaaaaaaaa aaaaaaantt 2070
```

<210> 77

<211> 997

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (619)

<223> n equals a,t,g, or c

<400> 77

```
ctcgccctcc tgactcttcc tgcagggtggc tcaggaagga ttcagcctgg ccacttggtc 60
aggactctgc cagcacccat ctgagactga cctcttccgg gcctttggac actatgacct 120
tgatgctgcc cttcaggcag gaaacagggc tgggtgccttt tttcacctgc atggccagct 180
tccttccctg gcagtggaga gggcagccaa caggttctaa tgtcagagcc atcctttacc 240
agggtggcct gcttgtccct gtcttgccct ccacatcact ctactttttg gaaggccatg 300
gctgattaaa gaagtctctg tagtttccca agcaaagtgg aatctagaaa cagtgaaaaa 360
agttcagata actttgaatt gcattcaaga agtacacttc tttcccatg tccgtggctc 420
ttggagtctc cgtgatgcca ggctagagtc tgattatata ataattcaaa atggtaactc 480
ccaaggtaat gctttcttcc atttcatcag gttcttttat cccactgca cccctctccc 540
ttctcccttg cctatctgga tggcttctca gaagctcggc cctagtcctc cctgccttgg 600
cgggggccag agcccactna ctgctgaggc agcactgctc tcgtcagctg tgttgccctt 660
amccaagtgt cttcagaggg ttatgagtta gagtagctgg cctggggaga ggggtgcctc 720
ctgggtttga tctttagggt ctgactttct gcagagaaga tgttttacag atgtgtcaaa 780
gctgatgtaa tgtggttggg ggaggaaatc cagacccaaa gtgtttgtca gctgggtgta 840
caactgccta tgtgatcctc tgtcttaaaa tgatttctgt ctgtgctgcg aaacaaagac 900
aaggtagagt gtttttcttt tttgtaataa tataaagctg tgtgtttctg attggatgat 960
tcactatgtg cattgttccy cctaagtgtc tttagta 997
```

<210> 78

<211> 1333

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1254)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1297)

<223> n equals a,t,g, or c

<400> 78

```
gagaggagct gctgcgcgcc caggaagcgc cggggcaggc cgagccgccg gccgccgccg 60
aggtgcaggg ggctggcaac gaaaatgagc ctgcgcaggc cgacaagagc caccgcggagc 120
agcgcragct tcggcctcgg ctctgtacca tgaagaaggg cccagtggtc tatggcttca 180
acctgcacag cgacaagtcc aagccaggcc agttcatccg gtcagtggac ccagactccc 240
cggctgaggc ttcaggggctc cggggcccagg atcgcatgtt ggaggtgaac ggggtctgca 300
tggaggggaa gcagcatggg gacgtggtgt ccgccatcag ggctggcggg gacgagacca 360
agctgctggt ggtggacagg gaaactgacg agttcttcaa gaaatgcaga gtgatcccat 420
ctcaggagca cctgaatggt cccctgcctg tgcccttcac caatggggag atacagaagg 480
agaacagtcg tgaagccctg gcagaggcag ccttgagag cccaggcca gccctggtga 540
gatccgcctc cagtgcacc agcaggagc tgaattccca agacagcccc caaaaacagg 600
actccacagc gccctcgtct acctcctcct ccgaccccat cctagacttc aacatctccc 660
tggccatggc caaagagagg gccaccaga aacgcagcag caaacgggcc ccgcagatgg 720
actggagcaa gaaaaacgaa ctcttcagca acctctgagc gccctgctgc caccagtgga 780
ctggcagggc cgagccagca ttccacccca ctttttcct tctccccaat tactcccctg 840
aatcaatgta caaatcagca cccacatccc tttcttgac aaatgatattt tctagagaac 900
tatgttcttc cctgacttta gggaaagtga atgtgttccc gtcctcccgc agtcagaaag 960
gagactctgc ctccctcctc ctactgagt gcctcatcct accgggtgtc cctttgccac 1020
cctgcctggg acatcgctgg aacctgcacc atgccaggat catgggacca ggcgagaggg 1080
caccctccct tcctccccc tgtgataaat gggccaggg ctgatcaaag aactytgact 1140
gcagaactgc cgytctyagt ggacagggca tygttatga cagacctktg gcagacacgt 1200
cttgttttca ttgatttttg ttaagagtgc agtattgcag agtctagagg aatntatggt 1260
tccttgatta acatgatttc ctggttgta catccanggc aggcagtggc tcagctttaa 1320
atgtgttttc cta                                     1333
```

<210> 79

<211> 560

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (542)

<223> n equals a,t,g, or c

<400> 79

```
caatggggct gaggtgtgt ccaactgaggc taagatgact gcctttcctg attggccttg 60
gcttttccat acattgtgtg acccttgccc tatgaccctt tggctgacct taccggaagc 120
catgacgaca gcagcctttt gccattagac gcagggtgat ggtgaggatt ccaaggggta 180
```

```

gacaaaactg gttaatctga actaggtgac tgttaccttg cgtgttttgt ggccaaacca 240
ccaccaaaaa cctcacactg tgatgtaagt acttagtgta aaactagtaa acatttttgt 300
aaaatgtaga aatgcatgta atcagttaag ttttatattt tacaatgttc tgtaaaataa 360
aacttagcga ggtaaatcga ataaaggagc agtcactctc taacagattg taggagaggt 420
ttagttggat ttagtctatt tgacttgccc ttaatttaat tttatggcaa atcacaaatg 480
tgtcgaaggt ttagcaatat aatagcaaag tcctactcca gtaaataaaa gttggtatgt 540
tngtacttaa ctttcaaaag                                     560

```

<210> 80

<211> 3203

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1116)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1443)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1942)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3188)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3201)

<223> n equals a,t,g, or c

<400> 80

```

cggtagcgct gggtagcggg cttcgggggg ctgcgctcgc ggctgcctgg actcagcagg 60
cccctggacc atgtcccgcg cctgcgggcc accgctcccg cctctctgct ttttcctttt 120
gttgctggcg gctgccgggt ctcgggccgg gggatacgag acatgcccca cagtgcagcc 180
gaacatgctg aacgtgcacc tgctgcctca cacacatgat gacgtgggct ggctcaaaac 240
cgtggaccag tactttttatg gaatcaagaa tgacatccag cacgccgggt tgtagtacat 300
cctggactcg gtcactctctg ccttgctggc agatcccacc cgtcgcttca tttacgtgga 360
gattgccttc ttctcccgtt ggtggcacca gcagacaaat gccacacagg aagtcgtgcg 420
agacctgtg cgccaggggc gcctggagtt cgccaatggt ggctgggtga tgaacgatga 480
ggcagccacc cactacgggt ccatcgtgga ccagatgaca cttgggctgc gctttctgga 540
ggacacattt ggcaatgatg ggcgaccccc tgtggcctgg cacattgacc ctttcggcca 600
ctctcgggag caggcctcgc tgtttgcgca ratgggcttc gacggcttct tctttgggag 660
ccttgattat caagataagt gggtagcgat gcagaagctg gagatggagc aggtgtggcg 720

```

```

ggccagcacc agcctgaagc ccccgaccgc ggacctcttc actggtgtgc ttcccaatgg 780
ttacaacccg ccaaggaatc tgtgtctggga tgtgtgtgtg gtcgatcagc cgctggtgga 840
ggaccctcgc agccccgagt acaacgcca ggagctgggtc gattacttcc taaatgtggc 900
cactgcccag ggccggtatt accgcacca ccacactgtg atgaccatgg gctcggactt 960
ccaatatgag aatgccaaca tgtgttcaa gaaccttgac aagctcatcc rgctggtaaa 1020
tgcgcaaggc aaaaggaagc agtgtccatg ttctctactc ccccccgct tgttacctct 1080
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tggcgggcaa cgtgggaccc tatggctccg gagacagtgc acccctcaat gaggcgatgg 1320
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gcngetcaga ggcttcaaag atcacttcac cttttgcaa cagctaaaca tcagcatctg 1500
cccgtcagc cagacggcgg cgcgcttcca ggtcatcggt tataatcccc tggggcgga 1560
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ccaggtgcct cgctggaagc cccaggcccc cgaccacag cccatcccca gaagatcctg 1800
gtccctgct ttaaccatcg aaaatgagca catccgggca acgtttgatc ctgacacagg 1860
gctgttgatg gagattatga acatgaatca gcaactcctg ctgcctgttc gccagacctt 1920
cttctggtac aacgccagta tnagtgaca acgaaagtga ccaggcctca ggtgcctaca 1980
tcttcagacc caaccaacag aaaccgctgc ctgtgagccg ctgggctcag atccacctgg 2040
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ttcgctgta cccaggacag cggcacctgg agctagagtg gtcggtgggg ccgatacttg 2160
tgggcgacac ctgggggaag gaggtcatca gccgttttga cacaccgctg gagacaaagg 2220
gacgcttcta cacagacagc aatggccggg agatcctgga gaggaggcgg gattatcgac 2280
ccacctggaa actgaaccag acggagcccc tggcaggaaa ctactatcca gtcaacaccc 2340
ggatttacat cacggatgga aacatgcagc tgactgtgct gactgaccgc tcccaggggg 2400
gcagcagcct gagagatggc tcgctggagc tcatggtgca ccgaagctgc tgaaggacga 2460
tggacgcgga gtatcgagc cactaatgga gaacgggtcg ggggcgtggg tgcgagggcg 2520
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cggggctcct ccgcgcacgc agttctcagg gctgcgcagg gacctgccgc cctcggtgca 2700
cctgctacag ctggccagct ggggccccga aatggtgctg ctgcgcttgg agcaccagtt 2760
tgccgtagga gaggattccg gacgtaacct gagcgcccc gttaccttga acttgaggga 2820
cctgttctcc accttcacca tccccgcct gcaggagacc acgctggtgg ccaaccagct 2880
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ggcctcagtt caatggaagg aggtggatgg ttaggtctgc tgggatgggc cctccaagcc 3060
caagcctcct gctccggggg cagaccagac tctgactctc ctcttgggct gctgccatta 3120
aaacgtact actaagaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 3180
aaatttanaa aaaaaaaaaa naa 3203

```

<210> 81

<211> 1710

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1424)

<223> n equals a,t,g, or c

<400> 81

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aagagccgaa cggataagag aagaggaggg cgcgkatggc gtcggggcgc cccgaggagc 60
tgtgggaggg cgtggtgggg gccgctgagc gcttccgggc cgggactggc acggagctgg 120
tgctgctgac cgcggccccc ccgcaccacc ccgcccgggc ccctgtgcct atgctgcca 180
tggtcgagga gccctggcgg aggcagcgcg ccgttgccct cagcacatcg cactggccca 240
cagggctgcc actgctgctc ggctcctgc gccccacca gcaccacagc caccagtc 300
cacacccagc ccaccccggc ctaccctggc cagagaggac aacgaggagg acgaggatga 360
gcccacagag acagagacct ccggggagca gctgggcatt agtgataatg gagggctctt 420
tgtgatggat gaggacgcca ccctccagga ccttccccc ttctgtgagt cagacccca 480
gagtacagat gatggcagcc tgagcgagga gaccccgcc ggcccccca cctgetcagt 540
gccccagcc tcagccctac ccacacagca gtacgccaag tccctgcctg tgtctgtgcc 600
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gccctcttcg cccgacctgg accgcctcgc ggcgagcatg cgcgcgctgg tgctgcgaga 720
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ccagaagctg aagcggaat attgaagtcc agggaggagg cgcgccgggc cgcgtccgcc 840
ccgtcccaca ctacgcccc gccccactcc cggggcctgc taatctgagg ccgatccggg 900
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aaagggcttg accagtctct acatagtcac cgtccgcttt tcctgagttc tccctcccaa 1260
ttggtccag cttcctgggg gcgtggccaa gccctcctct tcccagaatt ggcccggggc 1320
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cttgttccct gacccctca gggatggccc caaactgtcc ctgnccttg caccctttt 1440
cattggttcc atccatcccc acaacagcct gccaatcgaa gcccgccct gcattcagga 1500
tggtaccagc tcccgcctcc cgcgccccc ctccacaggt gccttaaagg gccctcgtca 1560
cccaagggtg ggcaggggc cctcactctc cggccctggt gtgggggaga gaggaggagg 1620
ttgggggatc ggcagttggg aggggcgctc tgagattaaa gatttttacc tctgagataa 1680
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1710
```

<210> 82

<211> 1379

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (280)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1365)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1378)

<223> n equals a,t,g, or c

<400> 82

```

aattcggcag agctgagccc cgggctgtgc agtccgacgc cgactgaggc acgagcgggt 60
gacgctgggc ctgcagcgcg gagcagaaaag cagaaccgcg agagtcctcc ctgctgctgt 120
gtggacgaca cgtgggcaca ggcagaagtg ggccctgtga ccagctgcac tggtttcgtg 180
gaaggaagct ccaggactgg cgggatgggc tcagcctgta tcaaagtcac caaatacttt 240
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tggatcctgg ccgacaagag cagtttcacg tctgtcctgc aaacctcctc cagctcgtt 360
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ggctgcatcg gcgcgtcaa cgargtccgc tgcctgctgg ggctgtamtt tgctttcctg 480
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gtaagcccc ctctccctcc ctcttcactg ggctggacca accatggggg tgattgactg 600
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gtgccgctgt ggcctgaaga tggggaagt ggcagtgcc gacatggcca tcccttttat 1320
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<210> 83

<211> 678

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (602)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (626)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (648)

<223> n equals a,t,g, or c

<400> 83

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cttgtgtgcc tgggtgcggga gctacggggc ccagggattg tgtttaaagt agtgcttcta 120
ccaacatgtc ccgtggttcc agcgccggtt ttgaccgcca cattaccatt ttttaccgcc 180

```

```

agggtcggct ctaccaagta gaatatgctt ttaaggctat taaccagggt ggccttacat 240
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aattattgga ttccagcaca gtgactcact tattcaagat aactgaaaac attggttggtg 360
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ccgatatttc tcagggtctac acacagaatg ctgaaatgag gcctcttggt tgttgatga 540
ttttaattgg tatagatgaa gagcaaggcc ctcagggtata taagtgtgat cctgcagggt 600
antactgtgg ggtttaaac cactgnagcg ggagttaaac aaactggngt caaccagctt 660
ccttgaaaaa aaagtgga 678

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<210> 84

<211> 2803

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (10)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (50)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (517)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (572)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1926)

<223> n equals a,t,g, or c

<400> 84

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tgtcagcaga gtccgtcaga cgtgagaagg gtgggagcgg cggactgtga acgctggtag 360
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cttccggtgt catagctgtg ggatccggaa gtaaaaacac aagccccgcs cccrrgaact 480
cggggaagccg gcgakaagtg tgaggccgcg gtagggnccg atcccgtcc ggagagaagt 540
ctgagtcgcg cagctctgca ggccgcgga antcgacagc gtcatggcag agcaggtggc 600

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```

cctgagcccg acccaggtgt gcgggatcct gcgggaagag cttttccagg gcgatgcctt 660
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gaagatctac cccaccatct ggtggctgtt ccgggatggc cttctgcccg aaaacacctt 780
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gtgccacccg taggcagcct ctctgctata agaaaagcag acgcagcagc tgggaccctt 2700
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<210> 85

<211> 1278

<212> DNA

<213> Homo sapiens

<400> 85

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atctttgtgc attggggcca cctatgacgt cacagactcc cgcatacccc atcagattgt 180
cgaccggcct gggcagcaga cctcagtcac tggcaggtgc tacgtgcagc cccagtrrgt 240
gtttgactca gtgaacgcca ggctccttct ccccggtggc gagtacttct ctgggggtgca 300
gctgccccca cacctttcac cctttgtgac cgagaaggaa ggagattacg ttccacctga 360
gaagctgaag ctgctggctc tgcagcgggg agaggaccca ggaaacctga atgagtcaga 420

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agaggaggag gaagaggacg acaacaacga aggtgatggt gatgaagagg gagaaaatga 480
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cctggaagag cagaggatgg aggggaagaa gcccagggtg atggcaggca ccttgaagct 600
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gatgatgaag aagcgggaga agtacctgta ccagaagatc atgtttggca agaggcgaaa 720
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cacacagttag gaccctgat tctcagggtg ctgtgatggg gtgagggtag ggggagcatt 1200
tgttattaaa tgactggact tttgtgcaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1260
aaaaaaccca cgcgtccg 1278

<210> 86

<211> 2585

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2573)

<223> n equals a,t,g, or c

<400> 86

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accocgagtg gtcccctttg gctcgattcc caggaaactc ctcctcaacc cctttggcat 120
cagcattaca agccaaagcc tcaatccagg gccctttcgt actcctaaag cagggataag 180
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tcccgagaa gagatccctg cctacatgtc tgtgcacga ctcctgagga agctgctaag 360
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cttaatttta attccatctc cagagagatt tgaggtgtat ttaagatgaa aaacaggata 2520
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<210> 87

<211> 385

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (385)

<223> n equals a,t,g, or c

<400> 87

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ttttatattt caactaaaag tatcaaaata tagctttcca gaaaaccccg aaccaaagtc 120
actgactaca tcaaagtcta ctacaccttg agaaaacaaa tgaacgaaaa tctattttcc 180
tcattcatta cccaacaat aataggactc cctatcgtaa ttattatcac tatgtttcca 240
agcattatat tcccatcacc taccgactr aatcaataat cgactscatc tccattccaa 300
caatgattag tgcactgaac atscaaaaca aatrttgatc catgccacaa caaaaaagga 360
caaactggag cccggatatt gatan

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<210> 88

<211> 2500

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (429)

<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (1088)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2480)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2482)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2491)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2497)
<223> n equals a,t,g, or c

<400> 88
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gccctgctgg tggagaccca gatgaaaaag ttggagatca aacttcggca ctttgaggag 180
ctggagacta tcatggaccg ggagcragaa gcactggagt atcagaggca gcagctcctg 240
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cagcacttcc aacagatgca ccaacagcag cagcagccac caccagccct gccccaggc 360
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ggagcccccc agcctggggc agtcccacca ggggttcccc cccctggacc ccatggcccc 600
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```

<210> 89

<211> 1409

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (841)

<223> n equals a,t,g, or c

<400> 89

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catcgatgag gctggccact gcatggagcc tgagaagtct ggtagctata gcagggtga 180
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```

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1409

<210> 90

<211> 1336

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (49)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1284)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1317)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1333)

<223> n equals a,t,g, or c

<400> 90

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<210> 91
 <211> 787
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (677)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (725)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (742)
 <223> n equals a,t,g, or c

<400> 91
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 acaagtg 787

<210> 92
 <211> 1657
 <212> DNA
 <213> Homo sapiens

<400> 92
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ggaaaaaaaa aaaaaaaaaa aaacycgggg gttttct 1657

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<210> 93

<211> 485

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (478)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (485)

<223> n equals a,t,g, or c

<400> 93

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aaan 485

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<210> 94

<211> 764

<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (202)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (565)
<223> n equals a,t,g, or c

<400> 94
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cactcatcag catggcccg angctggggg gcatcgggca taccacagca ggcccctatg 240
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caatcatctc agtggcgaag cacaccactt gattctatct ttttttaaca cattaaatct 720
gtttttaaag ataaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 764

<210> 95
<211> 707
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (45)
<223> n equals a,t,g, or c

<400> 95
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ccacgcgtgc catcatggcg caggatcaag gtgaaaagga gaaccccatg cgggaacttc 120
gcatccgcaa actctgtctc aacatctgtg ttggggagag tggagacaga ctgacgcgag 180
cagccaaggt gttggagcag ctacagggc agaccctgt gttttccaaa gctagataca 240
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gtatcaaata tgacccaagc attggtatct acggcctgga cttctatgtg gtgctgggta 480
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gaatcagcaa agaggaggcc atgcgctggt tccagcagaa gtatgatggg atcatccttc 600
ctggcgaata aattcccgtt tctatccaaa agagcaataa aaagtgttca gtgaaaaaaa 660
aaaaaaaaa aaaaaaaggg ggcccccttt tgggggtccc ctggggg 707

<210> 96

<211> 815
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (16)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (45)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (50)
 <223> n equals a,t,g, or c

<400> 96
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 caagcccgaa gatgcccccc attctctwag tgatggcggc gttaggggtt gagagaagg 180
 aatttggctc aacttcagtt gagaggggtgc agtccagaca gcttgactgc ttttaaatga 240
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 gaagaaaact gattctctat gacatgaaat gaaaatttta atgcattggt ataattacta 420
 atgtacgctg ctgcaggaca ttaataaaagt tgctttttta ggctacagtg tctcgatgcc 480
 ataatcagaa cacacttttt ttcctctttc tcccagcttc aaatgcaaat tcatcattgg 540
 gctcactttc aataactgca gtgtttcccg ccttgggctt gcagcagaaa aacctgacaa 600
 catagtgttt gctaaggcag taatttagac ttaccttat ttgtgattac tgtagtgtatt 660
 gattgattga ttactattaa ctacaaggta taatttacta tcaccttatt taaattttat 720
 gaattaattt gaatgttttt tacactaact aacttttccc aataaagtcc actatgaaac 780
 caccgacaaa aaaaaaaaaa aaaaaaaaaa aaaaaa 815

<210> 97
 <211> 658
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (627)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (634)
 <223> n equals a,t,g, or c

<220>

<221> misc feature
 <222> (635)
 <223> n equals a,t,g, or c

<400> 97
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<210> 98
 <211> 249
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (248)
 <223> n equals a,t,g, or c

<400> 98
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 atacctagat ctccagatgt catttcccct ctcttatttt aagttatgtt aagattacta 180
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 gggggccng 249

<210> 99
 <211> 752
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (612)
 <223> n equals a,t,g, or c

<400> 99
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<210> 100

<211> 3059

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (14)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (28)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (109)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3019)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3047)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3058)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3059)

<223> n equals a,t,g, or c

<400> 100

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<211> 1682
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (52)
<223> n equals a,t,g, or c

<400> 101
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ctttctggg gaaattatct ctggagggga aaaagatcca ttctacgtat ccttggtggag 720
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cagaatttga agtttggtc gcatccatac ttttctactg taaatatttc actctcctct 1620
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aa 1682

<210> 102
<211> 938
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (30)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (812)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (913)
<223> n equals a,t,g, or c

<400> 102
cccacgcgtc cgtccgggtg ctgcgcgcgn gacctggacg cagagaagcc agagactttc 60
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cgagtccgac tccctcaagg gtgacgcgag ctctgccctt taaccggaaa cgtctccctg 180
ctcaccacac cccgcgcgag acgcagtgtc gagcacacag ctaccggaca aagagtgcg 240
cccggagctg gagttatggc ggctacggag ccgatcttgg cggccactgg gagtcccgcg 300
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gtgggtcctt cgtcgccaga ggctcaccg cctgcccctg agccttccag tcccaacgcc 420
gcggtccctg aagccatccc tacgccccga gctgcggcct ccgcgccctt ggagctgcct 480
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gccccgcggc ctctagactc ggtcccgaag cgttccgcca gcgtttccg cagttccgct 600
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tgctcgccat cctkcccgag gcggctcggg cccggcggtt ccgcccgcgc acggatgtgc 780
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<210> 103
<211> 2012
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1993)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2002)
<223> n equals a,t,g, or c

<400> 103
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agttttggag aaagaagggt tacgttttca aacttacaga taacagttga catcaatgct 120
tctctttccc agaacaatct ggagtttgcc agaaaactct gtaaacagga gtcgtgctgt 180
gtgtgaactg taaactcttc tctccaggcg tcgaggggac ctttgcttta ctttgcagct 240
gggtacatc agacgtgtgc attggaacaa taaacttcct taactgggaa aagaatgctt 300
ctctgtcttc maaatarttc tgctatgtga catttttccc atcatgaatt ttacatcagt 360
gmtagctctt tgttttacgt gtttcattkg gcaggtcaca aaggctcttg gctaccacac 420
atacgtgcat acacacacac acacacacac acacacacac acacactcat aaaggatttt 480

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cttttctgct ttaccttta ttttcagtct acttggttg taatgaaagg tagagcctta 540
tttttgaact atatcccaac agaatcgaat ttccattttg ccaagaatta taaaaccctg 600
aggttttaaa attcagtttc ttttctgggg atttaacatg gaaggacttg gagggcaaat 660
ggscagtgat ttggaaaagg gaaaaacaaw tcatttcatt taaaattatt caataacat 720
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tatctctcac aaggctgtaa gcaattccta tgtccatata gcagtgagga aatggagatt 840
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rggtcatcag actgtcagcc ccagcactgg gagccgagta acacgcatgt tctcattaat 960
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cagggatttc atattaaaat ggtactatga tccaaacacc aaaagctgtg caagattctg 1080
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tgctgttggt aggcgaatgt aaagtctaga aaataatgca aatgtcacgg ctactctata 1560
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gtgctggagg gaggggattt aattttaatt ttaaaatgtt taggaaattt atacaaagaa 1920
actttttaat aaagtatatt gaaagttaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1980
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa 2012
```

<210> 104

<211> 1094

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (26)

<223> n equals a,t,g, or c

<400> 104

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atagatgatg cagaggcccc attggagaca cgtgaatggc gtgtgcggcc atcagttccc 120
ggctgggggg cagggtgtgc ttgggcccc gccctcggc cggcgtgtgc gagtgcgccc 180
ctggctgtga gtgttgaccg ttcctctccc ctgtacatag cmcgagccag tcctgagtgg 240
gtgactcctg agtgggtgac gcgcagacgg gatttctcag gtcatttgta tggtcgacat 300
gatggctgct gctttggctg ccaccacccc cgggcccage ctgtctgaaa ttcagggttt 360
aggccgaaaa acccggtggg gaggggtggg gagccggagm tctgtggcgg ggctggagg 420
ctggggtgca cttagtttg gggcgggacg ggagccggcg ttgtgactgg cgtggtctgg 480
ctgctgctcc cgaacggagg ggtcggggtt ggcttgcctg gccctcagag cccagtgggt 540
ggctctgact cggctcccta ctccctgcac ccagctgggc gcaattgggg cctgcggtcg 600
gaatgtatcc ctcccctcag ttttaacctg agctgccgaa cgcacagtgg gccgggggctg 660
aggctggggg aagcggggcc caattacgga tcccgggagt tacagggtgc gacgtgatgt 720
cgctctctct gtgcccagct ccctcctgg tctgagacta gctctggggg tggcgggggc 780
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ccccamacgc tgctcccgcct ccaccctgcc cgtgctgctg ctctgtgcct gctgtcagag 840
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ttgcggagag ccgcttatgg gtgtgtgtccg tccagacacc ttgtttcaag ggggatgggc 960
gtgagcgggc aagcagagca tccccaccgc tgagcaagaa ctttttcttg tttttaaac 1020
atcacgtcct catttcacat tggaataaag tgagtttttg aaacctgcga aaaaaaaaaa 1080
aaaaaaaaaa attc 1094

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<210> 105

<211> 2297

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (30)

<223> n equals a,t,g, or c

<400> 105

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agctcgtgcg ccgcccgtgc cgggtccggan attcccgggt cgacccacgc gtccgatctg 60
tcctgcacca tctgcctaata tccttcctca cagtctgtag ccatctgata tcctagggga 120
aaaggaaggc caggggttca catagggccc cagcgagttt ccaggaggt agagggatgc 180
gaggctaaca agttccaaaa acatctgccc cgatgctcta gtgtttggar gtgggcagga 240
tggaagaacag tgctgtttg ggggaaaaca ggaaatcttg ttaggcttga gtgaggtgtt 300
tgcttccttc ttgccagcg ctgggttctc tccaccagc aggttttctg ttgtggtccc 360
gtgggagagg ccagactgga ttattcctcc tttgctgatc ctgggtcaca cttcaccagc 420
cagggctttt gacggagaca gcaaataggc ctctgcaaat caatcaaagg ctgcaaccct 480
atggcctctt ggagacagat gatgactggc aaggactaga gagcaggagt gcctggccag 540
gtcggctcctg actctcctga ctctccatcg ctctgtccaa ggagaaccog gagaggctct 600
gggctgattc agaggttact gctttatatt cgtccaaact gtgttagtct aggcttagga 660
cagcttcaga atctgacacc ttgccttgct cttgccacca ggacacctat gtcaacaggc 720
caaacagcca tgcatttata aaggctcatca tcttctgcc cttttactgg gttctaaatg 780
ctctctgata attcagagag cattgggtct gggaagaggt aagaggaaca ctagaagctc 840
agcatgactt aaacaggttg tagcaaagac agtttatcat caactctttc agtggtaaac 900
tgtggtttcc ccaagctgca caggaggcca gaaaccacaa gtatgatgac taggaagcct 960
actgtcatga sagtggggag acaggcagca aagcttatga aggaggtaca gaatattcct 1020
tgcgttgtaa gacagaatac gggtttaatc tagtctaggc accagatttt tttcccgctt 1080
gataaggaaa gctagcagaa agtttattta aaccacttct tgagctttat cttttttgac 1140
aatatactgg agaaactttg aagaacaagt tcaaaactgat acatatacac atattttttt 1200
gataatgtaa atacagtgc catgttaacc taccctgcac tgctttaagt gaacatactt 1260
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taacaagaca aacttatgat aaagtatttg tctttagat cagggttttg ktttgkttt 1440
ttaattttta aatgcaaccc tgccccctcc ccagcaaagt cacagctcca tttcagtaaa 1500
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aagatctagt ccaatctttt tctagagaaa aagataatct gaagctcaca aagatgaagt 1620
gacttcctca aaatcacatg gtccaggaca gaaacaagat taaaacctgg atccacagac 1680
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cacaaacata agaactggtc ttctacactt tctctgaatc atttaggttt aagatgtaag 1860
tgaacaattc tttctttctg ccaagaaaca aagttttgga tgagctttta tatatggaac 1920
ttactccaac aggactgagg gaccaaggaa acatgatggg ggaggcagag agggcaagag 1980

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taaaactgta gcatagcttt tgtcacggtc actagctgat ccctcaggtc tgctgcaaac 2040
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aacagtttgc ccaggaactg ggggatcata tatgtcttag tggacagggg tctgaagtac 2160
actggaatth actgagaaac ttgtttgtaa aaactatagt taataattat tgcattttct 2220
tacaaaaata tattttggaa aattgtatac tgtcaattaa agtgtttttg tgtaaaaaaa 2280
aaaaaaaaaa actcgta 2297

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<210> 106

<211> 442

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (419)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (423)

<223> n equals a,t,g, or c

<400> 106

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tcgacccacg cgtccgcctg tgggacgcgg tgggtggccgt tgggtcggga gagtgagcgg 60
tatttgcmtc gtttttcttg cttgttttcc ccccgttaga ctttgtcggg agagcgcggg 120
tatgggccgc aagaagaaga agcagctgaa gccgtggtgc tggatttgta atagagattt 180
tgatgatgag aagattctta tacaacacca aaaagcaaaa cattttaaat gtcataatg 240
tcataagaag ttgtacacag gacctggctt agctattcat tgcattgcagg tgcataaaga 300
gacaatagat gctgtaccaa atgcatacct gggagaacag acatkgattg gaaatatatg 360
gtatgggaarg tattccagaa aaagatatkg atgaaagaag acgacttctt ggaacagana 420
acnccagaga gtccaaaaaa ag 442

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<210> 107

<211> 1019

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (995)

<223> n equals a,t,g, or c

<400> 107

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ttgatctgcg gctgtcgagg cctgaggcag tggaggctga ggctatgatg gcggccatgg 60
cgacggctcg agtgccgatg gggccgcggg gcgcccaggc gctctggcgc atgccgtggc 120
tgccgggtgtt ttgtcggtt ggcggcgccg cggcgccggc agcggcggag cagcaggtcc 180
cgctgggtgct gtggtcgagt gaccgggact tgtgggctcc tgcggccgac actcatgaag 240
gccacatcac cagcgacttg cagctctcta cctacttaga tcccggccctg gagctgggtc 300
ccaggaatgt gctgctgttc ctgcaggaca agctgagcat tgaggatttc acagcatatg 360
gcgggtgtgtt tggaacaag caggacagcg ccttttctaa cctagagaat gccctggacc 420
tggccccctc ctcaactggtg cttcctgccg tcgactggta tgcagtcagc actctgacca 480

```

```

cttacctgca ggagaagctc ggggccagcc ccttgcatgt ggacctggcc accctgcggg 540
agctgaagct caatgccagc ctccctgctc tgctgctcat tcgcctgccc tacacagcca 600
gctctgggtct gatggcaccg aggaagtcc tcacaggcaa cgatgaggtc atcgggcagg 660
tcctgagcac actcaagtcc gaagatgtcc catacacagc ggccctcaca gcgggtccgc 720
cttccagggt ggcccgatg tagccgtgg tggccggagg gctaggctcg cagctgtctac 780
aaaaacagcc agtatcacct gtgatccatc ctccctgtgag ttacaatgac accgctcccc 840
ggatcctgtt ctgggcccac aacttctctg tggcgtacaa ggaccagtgg gaggacctga 900
ctccctcac ctttgggggtg caggaaactc acctgactgg ctccctctgg aatgactcct 960
ttgccagcty tcactgacct atgaacgact ctttngtacc acagtgcacat taaagttat 1019

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<210> 108

<211> 711

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (642)

<223> n equals a,t,g, or c

<400> 108

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cttgaact tagtttacta tacatcttgc cctattaata tgttctctta acgtgtgcca 60
ttgttctctt tgaccatttt cctataatga tgttgatgtt caacacctgg actgaatgtc 120
tgttctcaga tcccttggat gttacagatg aggcagtctg actgtccttt ctacttgaaa 180
gattagaata tgtatccaaa tggcattcac gtgtcactta gcaaggtttg ctgatgcttc 240
aaagagctta gtttgyggtt tcctggacgt ggaacaagt atctgagttc cctggagatc 300
aacgggatga ggtgttacag ctgcctccct cttcatgcaa tctggtgagc agtgggtgcag 360
gcggggagcc agagaaactt gccagttata taacttctct ttggcttttc ttcattctgta 420
aaacaaggat aatactgaac tgtaagggtt agtggagagt ttttaattaa aagaatgtgt 480
gaaaagtaca tgacacagta gttgcttgat aatagttact agtagtagta ttcttactaa 540
gaccaataac aaatggatta tttaaaccaa gtttatgagt tggttttttt cattttcyat 600
ttgtatttta ttaagagtgc ttttcttatg gtgatttttt tnaattgcga ttgatattgg 660
tttgccata tggccccacc caaatcccca tcttggtatta taatccccat g 711

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<210> 109

<211> 743

<212> DNA

<213> Homo sapiens

<400> 109

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tcgagttttt tttttttttt ttttactttt taaaatttta ttgatgtacc acctgatcaa 60
agcatgggat attttaatag tattatacat aatatatttta catagaaaac tttacatagc 120
atttcatatt atataattct gcttattctt tcaaaaattt atacatccat tgggcaagga 180
atggttttca ttaaattacc aatattaaat gcacttaatc attgtgtata ggtaaacca 240
aagtaactat taactaactt ttaggcattt taaggaggta aaacatacat tttacacata 300
aatatttgat gcaaatatgc agataaaatt ttttaaaaat tagaactctg agtaaaacac 360
ctttgataga ttatattggt ttgttttgag agcaaggatt tccagatatg ttcattcttt 420
aaaacactca gctttggtt ctttgtttcc caaactgcaa agctgctgat aacaaaactc 480
caggattcca tgtgagtcca gctatgtcta ctttaacaca aatattaaaa cagaattcag 540
raaatgcagt attaaggatc cagcttctat tgaaaccaat atccatttgc atcataacaa 600
caaacatttg aatgagatgg tcacacttgt acttatcagc aggttccttt aataacaaag 660

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actactaaat gtatatacctt aatcacaaaa gaacaacaaa aaaaatacag gttttttttt 720
tttcatttcg tacaaaagtc acc 743

<210> 110
<211> 795
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (2)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (645)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (737)
<223> n equals a,t,g, or c

<400> 110
tnctaaatat cagatgtctt tgatgtaagg gtagggaatg gagaaatatt ttcaattgtg 60
tatttgtatt acaaagaact tgaaatttac tttcttagtt gattatatta aatgatgtat 120
atattatatg tggtttataa gctcaacact ggccattttt ttagttttat tggttaaattg 180
tattttttcta tgtttaatta taatagatct ggctttttct ggatagcata aagatcactg 240
aactatatat atataagara caagagttct attttagcac aaaggcattt tatattattt 300
attgaatoca taagtttggt ttcgtcaaaa acattccata ttatttctgc tcctttttat 360
ttgtatagtt tgttatttaa agaaatggca gtccttcctg ttcttaatac aataaaattg 420
aaataatgca cctagtaatg tggccgacat ctcttctcac caccatggac tgttttcaac 480
aacagttgat cttctgggtc gtgctgagag gcgcatgcat gtctttcgtc acgtcgggca 540
gcacacctgc tgtgaaatac tgctttcatc tacctcttca gaaggcttct tgcttggtga 600
caagtaccgc aaaggcttta ttctggactg gctatctcat aaaanggatt tctgtaagac 660
tttgagtggt cattccctca gaaccyaggt ttgtttctaa agccacggta ttgtccrrgr 720
rccctgtgt ktggggncag gtagctatcc ctcccatgtc attagtaatc ctttaggatt 780
ttaagggtaca atggg 795

<210> 111
<211> 1332
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (6)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1194)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1237)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1241)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1300)
<223> n equals a,t,g, or c

<400> 111
ncgggncagc agctcccagt gtgacctgac aaaaacacgt aggggcaggg acggtcccca 60
ccccagggga cacaaccctt ggtcttggac cagtagagga cacggagggt tcagaccctt 120
cctcagacc cccccacatc tgaaactgcc tcccccaac caccagcagc agcagggccc 180
tcctcccca ccagctctcc ccacagggcc cctcagcatc atggagaccc gcagcggggc 240
ttagccacc ctcaaaccga gggccccctg gcacctgggc tctggccgtg ttttctggcc 300
agagcccccac tttcctaact cgtgctccct tccgccttct tttccgtact gtgaagaaag 360
aactctccac cccagctccc accctgccct ggctgggtg gaggaactgt gcctccatcc 420
ccagaagaaa cagccccctc tgctgctggg gtgggactgt ctgtgtgccc tgtgggggtc 480
cgtgtgagca ggcccacctg gctccagacc cggcccaac ctgagacaga accaggctga 540
gccaggcctc cacccccacc ccggtttgct gggggctcct ccagccgcc ccatggraag 600
aggcctggta ccgctcacc cacagaggtc tgtgccagggt gcgcttctgc aggtggagcc 660
aagctctccc tgaggccaga ggcggggcct gggccgggag cccaggggaa ggccaggctg 720
gaccccggtc ycacaccac atccagcctg caggcctctc tgcatcctc tcacctccc 780
ttagctcccc ttcctctgca gtcacctca gctcccttc cttgcccgcc tctcccccg 840
ccgccccacc agttaaacgg atgaccaaag acctttctta tgccggaagc aaaaaccaa 900
actttttgtt ggctttttcc tttgtsgcct cccagcacc tgccctcca gtctccacc 960
ccggccccag gctggaagcc tccctccact taagttattg ttttaaacca aagtttacag 1020
tgtctgttgg tggccaagac cttctctctc caccctcct ccatccacc tgaggaccct 1080
ggggctcagt ggaggcaggg ccctgcccc cttcccttc cggctcctgg cccagcctgg 1140
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acggggagcc ctttcttccc tggaccctgg ggcttgnttc ntgggggggc tcttccaaga 1260
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aaggcaaaag ag 1332

<210> 112
<211> 743
<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (53)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (272)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (275)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (278)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (590)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (618)

<223> n equals a,t,g, or c

<400> 112

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gggtgcggatg gccagctcca ggatgaccg cgggaccg ctcacaaata aggtggccct 120
ggtaacggcc tccaccgacg ggatcggtt cgcacgccc ggcgtttggc ccaggacagg 180
gccacgtggt cgtcagcagc cggaagcagc agaatgtgga ccaggcgggtg gcacgctgca 240
rggggagggg ctgagcgtga cgggcacctg tncantgntg gggaaaggcgg aggaccggga 300
gcggctggtg gccacggctg tgaagcttca tggaggtatc gatatcctag tctccaatgc 360
tgctgtcaac ctttctttg gaagcataat ggatgtcact gaggagggtg gggacaagct 420
ctggatggac aaggaaaaag aggaaagcat gaaagaaacc ctgcggataa gaagggttagg 480
cgagccagag gattgtgctg gcatcgtgtc tttcctgtgc tctgaagatg ccagctacat 540
cactggggaa acagtgggtg tgggtggagg aaccccgctc cgcctctgan ggaccgggag 600
acagcccaca ggccagantt gggctctagc tcctggtgst gttcctgcat tcamccaytg 660
gscttttccc acctygytc amcttactgt tcacctcatc aaatcagttc tgccctgtga 720
aaagatccag cttccctgc cgt 743

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<210> 113

<211> 1690

<212> DNA

<213> Homo sapiens

<220>
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 <222> (1659)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1664)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1676)
 <223> n equals a,t,g, or c

<400> 113
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 ttggctgcag tccagctgcc agatggcttc aacctgctct gcccaacccc accacctccc 120
 ccagacacag gccccgagaa gctgccatca ctggagcacc gggactcccc ttggcaccga 180
 ggccccgccc ctgccaggcc taaaatgctg gttatcagtg gaggtgatgg ctatgaggac 240
 ttccgactca gcagtggggg cgccasagca gtgagactgt gggctcgagac gacagcacia 300
 accacctyct cctgtggagg gtgtgacctt gtctgccctg gccaggact sgcccgccca 360
 cctgccttca gcctgcttgc ctctccctag cccacacgca gactttgacc aggagtatcc 420
 agccagggga cacatgtgcy kgcrtgggct ctgcttgcct tcgcggaaga ttcctgatgg 480
 aacacccact ggccagccag gccatggctt ctcccagacc tctggctgcc ccggtgcttc 540
 cagtcgatgat cgggtggggg acatgtgggc tgaccaggac ctctgacctt ggagcttcta 600
 ccaaagacac agctgggtct ggaccccacg ggsstgggga gggccatgtg caatatttgg 660
 aggggttttct ggagggcagc aggaaggctg gggaattccc catgtacagt atttatgttt 720
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 ggggtgattt gaggaatga catgaggaag agaaacctat tcctgccctg gggaccaccc 840
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 tacagacaca cagtcacgca cactgcatgt ccaaggccct aaacattgcc cgttgacata 960
 aactttccag gggcccagcc tgatggggct gccctcagtc ctctagatca agatgctgac 1020
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 tgggtgggccc tttagtgggt ccctaatttg ggaacactga tggggccttg gacaggcctt 1140
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 tgcttcctg tgtctcatgc actggcacat atggtcacct tggagggcag acctaggagc 1260
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 gaccccccaa agctgagggg ctgaatgtag ctttttcaac agagaaggct cccacttgag 1380
 agcagcctct acctgacccc ctggaccaca gagagccact ctgaccctca gccccctcgc 1440
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 tttggttttg tttggggtgg gtgggtcatt gcggtcttag attatgtttc tcttgctacc 1560
 aaacagtcac gtattaaact tctttggatg atgaagttaa aagagtcaat aaatagaaac 1620
 accagatgac tgcaaaaaaa aaaaaaaaaa aaaaaaana aaanaaaaaa aaaaaanaaa 1680
 aaaaaaaaaa 1690

<210> 114
 <211> 620
 <212> DNA
 <213> Homo sapiens

<400> 114
ctctgggcct gggctctgggg gagaggggtg ccagggagac tcagctctcc ttgggggctg 60
gccagctgac tgaggggtaca caggattggg tctagacctt gatgcctggg tggagggccc 120
ttgtaagggg ccatagcctc ttcaggacca actggaggga gagttaggaa acaccagctc 180
ctgcctgggg cagtgaggga atgggagcag ctgtgggcgc ctcatctcag gcaagtcctc 240
cccaaacctt cagatgcagt gagacctggc ctccctgttg tgcttttcag actttgtttt 300
cagaatgctt ttatctcgag tgtgcccttc ggccctcaca agagcccctg gggagtaggt 360
ggtggcctgt gccgtcatcc ccatttcaaa gcaggagct gaggtcctgg gaggggaaaag 420
tgcttgctg aggtcccact gtgttagtgg gtgggcagga ctggaactcg gttctccaac 480
agcccagagc tcaactctttt acaccagag gtggagcagg tggcttaggg ggtgggtatg 540
tacttcacaa gccaatcccc ttcagccagg agctcctggg tgcatttccg tgtcagaaac 600
agtaccgagt cccacccct 620

<210> 115
<211> 542
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (392)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (412)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (511)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (521)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (535)
<223> n equals a,t,g, or c

<400> 115
tcgacccaag cgtccgcttc tcggccctt gtagaacctc tgtcaggttc agcctactcg 60
cctctactcc agcctccact ccggcctcca ccatgtccgt caggtgacct agaagtccta 120
caaggtgtcc acctccggcc cccgggcctt cagcagccgc tcctacacca gcgggcctgg 180
ctcccgcac agctcgtccg ccttctcccg ggtgggcggc asttccgggg gggcctgaac 240
agcagcatga gtgtggtcgg gggctacggc ggcggggccg gggatatggg ggcacacag 300
ccgtctcagt gaaccagagc ctgctgagcc cccttwaagc tggaatkga tcccaacatc 360

```

caagctgtgc gcaacccagg agaaggagca gntcaagacc ttcaacaaca anttggttc 420
gttcacgcac aagtgaagca ctggagcagc agaacaaatt tttggagacc aattggagct 480
tcttaaagca gcagaagacg cgcggagaac ntagacaaat ntgcgagagt aaatnagaac 540
tt
542

```

```

<210> 116
<211> 525
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (420)
<223> n equals a,t,g, or c

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```

<220>
<221> misc feature
<222> (424)
<223> n equals a,t,g, or c

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```

<220>
<221> misc feature
<222> (517)
<223> n equals a,t,g, or c

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<400> 116
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atactgccat cgacgggata ccggtatacc gcgaggaact gatgatcgtc acgccacaag 180
gatatgcgcc agtaaccctg gccagtcagg ttaatggcag taacatttat gccttccgcg 240
ccaattgttc gtatcgtcgc cacttcgaga gctggtttca tgctgacggt gccgctcccg 300
gaactatcca tgagatggag tcttatcacg gaatgttggc ctgtgtgatc gcaggagcag 360
gcattgcgct tattccgcgc tctatgctgg aaagtatgcc ggggcacac cargttgaan 420
cgknggccgt tagctgagca atggcggttg ttaacaacct ggctggtctg gccgtcgttg 480
tgcgaaaaaa cgttccgctc gaaggggggc ccggtancca attcg
525

```

```

<210> 117
<211> 728
<212> DNA
<213> Homo sapiens

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<400> 117
aacgagcgcc tgctaggatc agcgggtggtg gttccgcgat ggtagggcggc ggcgggggtcg 60
gcggcgccct cctggagaat gccaaacccc tcatctacca gcgctctggg gagcggcctg 120
tgacggcagg cgaggaggac gagcaggttc ccgacagcat cgacgcacgc gagatcttcg 180
atctgattcg ctccatcaat gacccggagc atccactgac gctagaggag ttgaacgtag 240
tagagcagggt gcgggttcag gttagcgacc ccgagagtac agtggctgtg gctttcacac 300
caaccattcc gactgcagc atggccaccc ttattggtct gtccatcaag gtcaagcttc 360
tgcgctccct tcctcagcgt ttcaagatgg acgtgcacat tactccgggg acccatgcct 420
cagagcatgc agtgaacaag caacttgcat ataaggagcg ggtggcagct gccctggaga 480
acacccaact cttggagggt gtgaatcagt gcctgtcagc ccgctcctga gcctggcctt 540

```

tgacccctca gctgcatac tggatcctg gtcccagctc ctgccagggc tgttaccgtt 600
gttttcttga atcactcaca atgagaaact aacattttgc tttttgtaat aaagttaatt 660
tatattcarw tcaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa acccgggggg 720
gggcccccc 728

<210> 118
<211> 948
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (920)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (944)
<223> n equals a,t,g, or c

<400> 118
agaagtacgg acccctgaag cccctgccac agaccccgca cctggaggas gacttgaagg 60
aggtgctgcg ttctgaggct ggcatcgaac tcatcatcga ggacgacatc aggcccgaga 120
agcagaagag gaagcctggg ctgcggcgga gcccatcaag aaagtccgga agtctctggc 180
tcttgacatt gtggatgagg atgtgaagct gatgatgtcc aactgcccc agtctctatc 240
cttgccgaca actgcccctt caaactcttc cagcctcacc ctgtcaggta tcaaagaaga 300
caacagcttg ctcaaccagg gcttcttgca ggccaagccc gagaaggcag cagtggcccc 360
gaagccccga agccacttca cgacacctgc ccctatgtcc agtgcctgga agacgggtggc 420
ctgcgggggg accagggacc agcttttcat gcaggagaaa gcccggcagc tcttggggcg 480
cctgaagccc agccacacat ctgggaccct catcttgtcc tgagggtgtg aggggtgtcac 540
gagcccattc tcatgtttac aggggttgtg ggggcagagg ggtctgtga atctgagagt 600
cattcagggtg acctcctgca gggagccttc tgccaccagc ccctccccag actctcaggt 660
ggagcaacag ggccatgtgc tgccctgttg ccgagcccag ctgtggggcg ctcctggtgc 720
taacaacaaa gttccacttc cagggtctgcc tggttccctc cccaaggcca caggagctc 780
cgtcagcttc tccaagccc acgtcaggcc tggcctcatc tcagaccctg cttaggatgg 840
gggatgtggc cagggtgtct cctgtgtctc ccctctcttg gtgcattttt ttggaagaat 900
aaaattgcct ctctctttgn aaaaaaaaaa aaaaaaaaaa gggngggc 948

<210> 119
<211> 211
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (123)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (125)

<223> n equals a,t,g, or c

<400> 119

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tcgacccacg cgggtccgctt ggtgggggtcg gctgctttct cgcgttttccc cccaaccccg 60
tccggcctcg cccagcgttt ccacgcggaa ccaactgccg gaggcgcggc gcggcgtcga 120
gcngngcgag tgtgaggaaa ccgccgcctc agccgagcgc gcgggcccgc ccagggcggt 180
agttttcggc gcgcagtcgc ggtcccccg c 211
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<210> 120

<211> 1308

<212> DNA

<213> Homo sapiens

<400> 120

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tcgacccacg cgtccggact gttctaagtg agttcgggtg ggggagcttc acgaggggag 60
gctgctctgt gaaggaaccg cctttctctc cgcggtgtctc acccttttct ccccatatct 120
gtttggacat gagctgaggg cacggtcgcg ggcggtcagc ctgttcgcag ctacggcgag 180
gaggggcgcg attgytcctt gttgccgctc cgcttagtgg ccgcgtccat tccgcgcggt 240
gtcccgatth tagggtagg gagaagtgtc agcttcaggc atcgcgaggc gtggcgggcc 300
catggccccc tagggaggcg ccccgcggtt ggtactgctg ttcagcggca agaggaaatc 360
cgggaaggac ttcgtgaccg aggcgctgca gagcagactt ggagctgatg tctgtgctgt 420
cctccggctc tctggtccac tcaaggaaca gtatgctcag gagcatggct tgaacttcca 480
gagactcctg gacaccagca cctacaagga ggcttttcgg aaggacatga tccgctgggg 540
agaggagaaa cgccaggctg acccaggctt cttttgcagg aagattgtgg agggcatctc 600
ccagcccatc tggctggtga gtgacacacg gagagtgtct gacatccagt ggtttcggga 660
ggcctatggg gccgtgacgc agacgggtccg cgttgtagcg ttggagcaga gccgacagca 720
gcggggctgg gtgttcacgc cagggggtgga cgatgctgag tcagaatgtg gcctggacaa 780
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gttgagaaac ctgatagaat ttatccgctc cagactttag ttagtaggtt ctaggagtga 900
gctggggcct gctgaggtgg ggggtgggct gactctgcaa aatgggggtg tccccgatc 960
ctggccgagg tgaggaacag acaggggggg tctagattct gagggggttg gtggatattg 1020
ggcaaggcag gaaacctctg gagacctcat tttctccatg gggaagacag ccatgctctt 1080
caggaggaga ctccaagggc aaaggagggt gtcttggtg tgcttgaagg cgaaacctg 1140
ccatatcccc agtgccagtc ccctcagcct gtggtggcct tgcatcctga ctggatgttc 1200
tcagcccctt gttctgggca agaaccaga gctcccaggt gtggatacta ataaacctct 1260
tggagcacia aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaagg 1308
```

<210> 121

<211> 2516

<212> DNA

<213> Homo sapiens

<400> 121

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gattgacatt ccagtgaat gatgggagtt aattgattta atttagatta gttgaaaatt 60
attacaaaat attctaaaag ggttttttgt ggtacttcaa gaaacctgat tagttttgat 120
ctattgaaat cacaaaagta gaacagggcw ytttattttt gtataattta ggattaggta 180
tgcttctttt ttctaacaag tcatgttttc taacccttct ttcactaagc aaaccagaac 240
agatttgaaac tgttatgggt tatatatttag tatggagatc agctcagatg acattaaaaa 300
tgccgtagtg ttattcttgt atgccaaatc tttttttccc caaaatttag actttaattt 360
tatttactgt tataatatth gttttcttag attaggtagg aaatcttaat ttggccaccg 420
cctactttga caagtaaata ttacatcata cgattttgca acattaaatt agaactag 480
```

```

aaactaaaaa attatgtttc agtgaatgct acaactaagc attttttttt ttttaagaaa 540
acaattgtat tatgttttgt tgccttgcca ctttgagtat cttatctgaa aatctgttcc 600
ttgccatggt tttctcctgt taacataaac tatgtgccct gtgaatttct ggggactgaa 660
tttgaaattg ctccctgcaa ccgtttgtgg cctggcgtgt atctgaatgc ctgaatatct 720
ccccgctgaa tgaatttcgt attctgccct gaattcactc ggggtatattg attggctgga 780
tgatcttggt gccgccact tgacgtttcc agaagagtca ccgaagaaa gaaccaggag 840
tgtagaggat gatgaggagg gtcacctgat ctgtcagagt ggagacgtac taagtgcaag 900
atgtatagaa tatttttcaa cacttattaa cttttcagat aacataatct atatatagat 960
taagctttca gggatttgga aatctttttt tctttctctt ttttgttttt gttttatttt 1020
tccatttctt ttggtggggg ggattgtatt tttgctttct tttagaaagt aatgtttgtt 1080
atatagaact tccagaacag taatcaaatt aatgaaatta gacctataa ttatgttttt 1140
tgatgggtgt gaccaataaa atatctagtg ataaggaaat ttgtagcatc aactagaata 1200
atctacattg atagcattta ttgtgataag tacattgttt ccacttcttg atatgactga 1260
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cttatttgtg cagtctgact acacagaggc gtataatccc aaaataaaac gtgatgaacg 1740
caccttaata aatccagata ttaaagttgt agactttggt agtgcaacat atgatgacga 1800
acatcacagt acattggtat ctacaagaca ttatagagca cctgaagtta ttttagccct 1860
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tgggtttacc gtatttccaa cacacgatag taaggagcat ttagcaatga tggaaaggat 1980
tcttggaact ctacaaaac atatgatata gaaaaccagg aaacgtaaat attttcacca 2040
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tcctttcttc gaccttctga agaaaagtat atagatctgt aattggacag ctctctcgaa 2280
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taaatcttta acatttttat attgccatgt ttattttgtt tgggtaattt ggttcattaa 2400
gtacatagct aaggtaatga acatctttt cagtaattgt aaagtgattt attcagaata 2460
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<210> 122

<211> 1139

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1053)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1124)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1125)

<223> n equals a,t,g, or c

<400> 122

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ggggccggag ccgggtgcgg atttgctggg gctgagtcgg gggcgcgcg gccctgacct 120
ctgccctctg acctctcccc tagcaggcga ccatggggaa cgtgttggct gccagctcgc 180
cgcccgacag gccgccaccg ccgcctgcgc cggccctcgt ggggctgccg ccacctccgc 240
cctcgccgcc gggcttcacg ctgccgccgc tgggaggcag cctgggggcc ggcaccagta 300
cgaktcgarg ttcggaacgg acccccgggg ctgcaaccgc cagcgccctca ggggccgccg 360
aggatggggc ctggggctgc ctgcccacc cgggcacatt cgaggagtgc caccggaagt 420
gcaaggagct gtttccatt cagatggagg gtgtcaagct cacagtcaac aaagggttga 480
gtaaccattt tcaggtcaac cacacagtag ccctcagcac aatcggggag tccaactacc 540
acttcggggc cacatatgtg gggacaaagc agctgagtcc cacagaggcg ttccctgtac 600
tgggtgggtga catggacaac agtggcagtc tcaacgctca ggtcattcac cagctggggc 660
ccggtctcag gtccaagatg gccatccaga cccagcagtc gaagtttgtg aactggcagg 720
tggacgggga gtatcggggc tctgacttca cagcagccgt caccctgggg aaccagacg 780
tcctcgtagg ttcaggaatc ctctagatcc actacctcca gagcatcacg ccttgccctg 840
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tagctgggaa atacacattg aacaactggg tggcaacggg aacgttgggc caggcgggca 960
tgcacgcaac atactaccac aaagccagtg accagctgca ggtgggtgtg gagtttgagg 1020
ccagcacaag gwtgcaggac accagcgtct ccnttsggg accagcttgg aacttgccca 1080
aggccaacc tcytctttca aaggstctgt tgggataagc aaannggat tcgtggggg 1139
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<210> 123

<211> 2114

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1966)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2039)

<223> n equals a,t,g, or c

<400> 123

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cctagcgcg ccacaccttt actccagaga tcatggctgc cgaggatgtg gtggcgactg 120
gcgccgaccc aagcgatctg gagagcggcg ggctgctgca tgagattttc acgtcgccgc 180
tcaacctgct gctgcttggc ctctgcatct tcctgctcta caagatcgtg cgcggggacc 240
agccggcggc cagcgcgac agcgacgacg acgagccgcc ccctctgccc cgctcaage 300
ggcgcgactt caccgccgc gagctgcggc gcttcgacgg cgtccaggac ccgcgcatc 360
tcatggccat caacggcaag gtgttcgatg tgaccaaagg ccgcaaattc tacgggcccc 420
aggggccgta tgggtctttt gctggaagag atgcatccag gggccttgcc acattttgcc 480
tggataagga agcactgaag gatgagtacg atgaccttcc tgacctcact gctgcccagc 540
aggagactct gagtgactgg gagtctcagt tcactttcaa gtatcatcac gtgggcaaac 600
```

```

tgctgaagga gggggaggag cccactgtgt actcagatga ggaagaacca aaagatgaga 660
gtgcccggaa aaatgattaa agcattcagt ggaagtatat ctatTTTTgt atTTTgcaa 720
atcatttgta acagtccact ctgtctttaa aacatagtga ttacaatatt tagaaagttt 780
tgagcacttg ctataagttt ttttaattaac atcactagtg acactaataa aattaacttc 840
ttagaatgca tgatgtgttt gtgtgtcaca aatccagaaa gtgaactgca gtgctgtaat 900
acacatgtta atactgtttt tcttctatct gtagttagta caggatgaat ttaaagtgt 960
ttttcctgag agacaaggaa gacttgggta tttcccaaaa caggtaaaaa tcttaaatgt 1020
gcaccaagag caaaggatca acttttagtc atgatgttct gtaaagacaa caaatccctt 1080
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gcagtgttcc aaagactttg gtatggatta agcgtgttcc agtaacaaaa tgaaactctc 1200
aaacagagct cagctgcaaa aaagcatatt ttctgtgttt ctggactgca ctgttgcctt 1260
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ttttcttggt aactgtgttt tatgatttta cctcaaatca gaaaacaaaa tgatgtgctt 1860
tggtcagtta ataaaaatgg ttttaccac taaaaaaaaa aaaaaaaggg cgccgctct 1920
aaaggatccc tcgaggggcc caagcttacg cgtgcattgc acgtcntagc tctctcccta 1980
tagtgagtcg tattataagc taggcactgg ccgtcgtttt acaacgtcgt gactgggana 2040
tctgctagct tgggatcttt gtgaaggaac cttacttctg tgggtgtgaca taattggaca 2100
aactacctac agag 2114

```

<210> 124

<211> 583

<212> DNA

<213> Homo sapiens

<400> 124

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gcccgcccta ttcccttggg cttttaaaaa gcgtcttggg tggaggtggg gcaggtgctc 60
accaagcccc cagtaaccca agttgcatgt atccccaggg cacttttTgt attccctgc 120
ttgtgactgc acaccgggac cccactcaat tcaaagaccc agactgcttc aaccctacca 180
acttcctgga caagggaag ttccaggga atgatgcttt catgcccttt gcctcaggtg 240
caggcagagg aggaagggga ccagcctgga ctggctctgg ggtacctggg gctcactgtg 300
cacctgtgta cccggcaaaag cagatgtgcc tgggcacagg cctggcccac tcgggtatct 360
tcctattcct tacggccacc ttacagaggt tctgcctgct ccctgtggta cgccctggca 420
ccatcaacct cacctgcagt gcaactggcct gggcagtgtc ccccagact tccagctcca 480
gccagtggcc tgctgaggtc aggtccact atggtgggct cactggccct caaacctcca 540
taccctccts ggtcaataaa ggcctaaat tgcaaaaaaa aaa 583

```

<210> 125

<211> 1987

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (7)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (14)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (517)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1960)

<223> n equals a,t,g, or c

<400> 125

cgctacngtc cgantcccgg gtcgaccac gcgtccgatg gcggcggagg aacctcagca 60
gcagaagcag gagccgctgg gcagcgactc cgaagtgtta actgtctggc ctatgatgaa 120
gccatcatgg ctcagcagga ccgaattcag caagagattg ctgtgcagaa ccctctggtg 180
tcagagcggc tggagctctc ggtcctatac aaggagtatg ctgaagatga caacatctat 240
caacagaaga tcaaggacct ccacaaaaag tactcgtaca tccgcaagac caggcctgac 300
ggcaactgtt tctatcgggc ttctcgattc tcccacttgg aggcactgct ggatgacagc 360
aaggagttgc agcgggtgaga aggggtggga ctgggcaccg aggcaggtgg gtgtytacct 420
cctccccggg cgagtaggat gtgtctcgag taggggtgtc ycctccttcc cgggcgatgg 480
gctggactct ggccttgcca rgcggggcag tgctgtntcg gccctggcgt ctgggctggg 540
cgaggagccc atgctgggcc cgcccttcca tcccaccccc aggttcaagg ctgtgtctgc 600
caagagcaag gaagacctgg tgtcccaggg ctctactgaa ttcacaattg aggatttcca 660
caacacgttc atggacctga ttgagcaggt ggagaagcag acctctgtcg ccgacctgct 720
ggcctccttc aatgaccaga gcacctccga ctaccttgtg gtctacctgc ggctgctcac 780
ctcgggctac ctgcagcgcg agagcaagtt ctctcagcac ttcacgcagg gtggacggac 840
tgtcaaggag ttctgccagc aggaggtgga gcccatgtgc aaggagagcg accacatcca 900
catcattgcg ctggcccagg ccctcagcgt gtccatccag gtggagtaca tggaccggcg 960
cgaggggcgc accaccaatc cgcacatctt ccctgagggg tccgagccca aggtctacct 1020
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tgccctgctg cccccctctg ccaggcgcta gacatgtaca gaggtttttc tgtggttgta 1140
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tccccaacag gagcaggttt gaggggccag gcctcttggg ggcccctcct gcttcgttgg 1380
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ctctgcattg cctgcctttt tgcccttacc tcttttcttc cccgccccct gcacattcgg 1860
gktctcagcc cccaggctgt gagctccttg gggcaggccc tcaataaatg tgaaactgct 1920

gctgcaaaaa aaaaaaaaaa aaaaaaaggg ggccgcttan agatcctcaa gggccaagta 1980
 cggtgat 1987

<210> 126

<211> 1451

<212> DNA

<213> Homo sapiens

<400> 126

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ggtcgaccca cgcgtccgag atggcggagc gcgggtacag cttttcgctg actacattca 60
gcccgtcttg taaacttgtc cagattgaat atgctttggc tgctgtagct ggaggagccc 120
cgcccgctgg aattaaaagct gcaaatggtg tggatttagc aactgagaaa aaacagaaat 180
ccattctgta tgatgagcga agtgtacaca aagtagaacc aattaccaag catataggtt 240
tggtgtacag tggcatgggc cccgattaca gagtgcctgt gcacagagct cgaaaactag 300
ctcaacaata ctatcttggt taccaagaac ccattcctac agctcagctg gtacagagag 360
tagcttctgt gatgcaagaa tatactcagt cagggtggtg tcgtccattt ggagtttctt 420
tacttatttg tggttggaat gagggacgac catatttatt tcagtcagat ccatctggag 480
cttactttgc ctggaaagct acagcaatgg gaaagaacta tgtgaatggg aagactttcc 540
ttgagaaaag atataatgaa gatctggaac ttgaagatgc cattcataca gccatcttaa 600
ccctaaagga aagctttgaa gggcaaatga cagaggataa catagaagtt ggaatctgca 660
atgaagctgg atttaggagg cttactccaa ctgaagttaa ggattacttg gctgccatag 720
cataacaatg aagtgactga aaaaatccaga atttcagata atctatctac ttaaacaatg 780
ttaaagtatg ttttgttttg cagacttttt gcatacttat ttctacatgg tttaaatcga 840
ctgtttttta aatgacactt ataaatcccta ataaactgtt aaaccacact tccagccttt 900
taggagttgc taaaatttta acagttatgt ccygcttttt atcacagttg atttctgaag 960
actayattgc caagcagaat gatgaaatga ctttttcggt gtcaggcaat tttggttaag 1020
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tgatttttgg aaaaaacatg actgcttcta gagctgggag gatctgcaga ctttcacgga 1140
ttcatggaac aagaaaagaa gcataggtac ttttaggtgc cattaggtat tgatcagtga 1200
aatcctaggg tgctctatga gattgtacta ggcctatgaa gagtggtaag ccaaataggt 1260
ctccatggga gatacattat gtaataaat aaacaatggt ttgctggttc ctgttggtgt 1320
ctccacaagt aggtaaacat gtttaagga acccggttc ttagattttg ttagactttt 1380
taaactcaag gatgagcata agtgcttgaa ataaatgct aatacttaag tgtcaaaaaa 1440
aaaaaaaaa a 1451

```

<210> 127

<211> 1234

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (857)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1204)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1226)

<223> n equals a,t,g, or c

<400> 127

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aggttcccag ctagccagta aattctttaa agacaagcat tgtacccttt gcctcagtgt 60
gccagcacc aacctggcac atgctctatt catgttttcc atgagtgttt catgttagag 120
gtgtattttg tacacagggt ttatgctggg ggctcagaga gaagtggaca gcagattgtt 180
ggccctccca ggaagaaaag tcccaacgag ctggtgggat gatctcttta aagggtccaa 240
agagcatgga gctgtagctg tggagcgagt gaccaagagc cctggagaga ccagtaaacc 300
gagaccattt gcaggagggt gctaccgcct tggggcagca ccagaggaag agtctgccta 360
tgtggcagga gaaaagaggc agcattccag ccaagatgtt catgtagtat tgaaactctg 420
gaagagtgga ttcagcctgg ataattggaga actcagaagc taccaagacc catccaatgc 480
ccagtttctg gactctatcc gcagagggga ggtgccagca gagcttcgga ggctagctca 540
cgggtggacag gtgaacttgg atatggagga ccatcgggac gaggactttg tgaagcccaa 600
aggagccttc aaagccttca ctggcgaggg tcagaaactg ggcagcactg ccccaggtg 660
ttgagtacca gctctccagc ccaacaggca gaaaatgaag ccaaagccag ctcttccatc 720
ttaatcgacg aatcagagcc taccacaaac atccaaattc ggcttgcaag cggcgggagg 780
ctggtgcaga aatttaacca cagccacagg atcagcgaca tccgactctt catcgtggat 840
gcccggccag ccatggntgc caccagcttt atcctcatga ctactttccc gaacaaagag 900
ctggctgatg agagccagac cctgaaggaa gccaacctgc tcaatgctgt catcgtgcag 960
cggttaacat aaccgcccag ccagctgcct ggccctccctc ctgtgtttcc catggccagt 1020
ggccatgcc catggggatc gcccctcctg ccccttctgt cacaccagc agtccagtgc 1080
aacgtctcct ccatagctct gggttcttag atcttggttg gacgtttgtt ttctccttag 1140
ttgcatttcc tgggtttttg tgatgatcaa tggactttaa tgaaaaaaaa aataaaaaa 1200
accnaaaggg gggcccggtc ccaatncccc cctt 1234
```

<210> 128

<211> 863

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (840)

<223> n equals a,t,g, or c

<400> 128

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cccacgcgtc cgcaggcgcg ctcggtctgc cgctggctct tcgcacgcgg ccatggccga 60
ctccgagctg cagctggttg agcagcggat ccgcagcttc cccgacttcc ccaccccagg 120
cgtggtattc agggacatct cgcccgctct gaaggacccc gcctccttcc gcgcgcccat 180
cggcctcctg gcgcgacacc tgaaggcgac ccacgggggc cgcacgcact acatcgagg 240
cctagactcc cgaggcttcc tctttggccc ctccctggcc caggagcttg gactgggctg 300
cgtgctcatt cgaaagcggg ggaagctgcc agggcccaact ctgtgggcct cctattccct 360
ggagtacggg aaggctgagc tggagattca gaaagacgcc ctggagccag gacagagggg 420
ggtcgtcgtg gatgatctgc tggccactgg tggaccatg aacgctgcct gtgagctgct 480
gggcgcgctg cagctgagg tcttgagtg cgtgagcctg gtggagctga cctcgcttaa 540
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gggcctccca gcccaacatc tccagctgga tcccagggaa atatcagcct tgggcaactg 660
cagtgaccag gggcaccggc tgcccacagg gaacacattc ctttgctggg gttcagcgcc 720
tctcctgggg ctggaagtgc caaagcctgg ggcaaagctg tgtttcagcc aactgaacc 780
```

caattacaca cagcgggaga acgcagtaaa cagctttccc acaaaaaaaaa aaaaaaaaaan 840
 aaaaaaaaaa aaaaagggcg gcc 863

<210> 129

<211> 1238

<212> DNA

<213> Homo sapiens

<400> 129

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 ccctccctgc ccctgcccta gctgctgtgt gttcagttgc cttctttcta cctcagccgg 180
 cgtggagtgg tctctgtgca gttagtgcc cccacacac ccgtctcttg attgagatgt 240
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 tcccggtga ctggcagttt tcacggtcta gggccgagac gatggcatgg ggcctagagc 480
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 cttaacatcc ttatctgtgt ccgccacgga ggtgactgag ctgctagcga gttgtcctgt 660
 cccaggtact tgagtttttg aaaagctgac tcacgcccat ccatctcaca gcccttccct 720
 ggggacagtc gcttccgcct tgacacctca ctctcagttg aataactcaa gcttgggtcat 780
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 tctgtcctgt tggctgcttg cttccagctc cccccaatct ccacgcagc gggttcctcc 1140
 tgtcttttct acagtgtcat aaaacatcct gccctaccc tctcccaaag gtcaatttta 1200
 attctyawca agaagattta tgaggagaag aaaaagaa 1238

<210> 130

<211> 379

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (373)

<223> n equals a,t,g, or c

<400> 130

tggtttggga gctgccaggc tcctgggagg atcgcagtca gcagagcagg gctgaggcct 60
 gggggttagga gcagagcctg cscatctgga ggcagcatgt ccaagaaagg gaggtaggt 120
 gcagcraagg acccaggggc agagccacgc tggggatgga ccccttcag gacacgctgc 180
 ggyggctgcg tgaggccttc aactgagggc gcacgcggcc ggccgagttc cgggctgcgc 240
 actccaggcg ctggggccact tccttcaaga aaacaagcar cttctrcgm acgtgctggc 300
 ccaggaaactg cataagccag ctttcgaagg cagacatata tgagtcatcc ttgcccagaa 360
 cgaggttgaa tangctctt 379

<210> 131

<211> 1786

<212> DNA

<213> Homo sapiens

<400> 131

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cctgggcgct aagatggcgg cggcgtgagt tgcattgtgt gtgaggatcc cggggccgcc 60
gcgtcgctcg ggccccgcca tggccgtcac catcacgctc aaaacgctgc agcagcagac 120
cttcaagatc cgcattggagc ctgacgagac ggtgaagggtg ctaaaggaga agatagaagc 180
tgagaagggt cgtgatgcct tccccgtggc tggacagaaa ctcatctatg ccggcaagat 240
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catggtgacc aagaccaaag ccggccaggg tacctcagca cccccagagg cctcaccac 360
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gcgggaccag cccagttcc agaacatgcg gcaggtgatt cagcagaacc ctgcgtgct 840
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cctggtcatc caggcctatt tcgctgtgta aaaaaatgag aacttggctg ccaacttcct 1140
cctgagtcag aactttgatg acgagtgatg ccaggaagcc aggccaccga agccccacc 1200
ctacccttat tccatgaaaag ttttataaaa gaaaaaatat atatataatc atgtttatct 1260
aagaaatgga aaaaaaatc aaaaaatctta aaaaaacaag caaacagtcc agcttcctgt 1320
cctcctaaag tggccccgtg tcccatctcc cgggccagac agctgtcccc ccgtcctcct 1380
ccccagccca gcctgctcag agaagctggc aggactggga ggcgacagat ggccccctct 1440
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ccgaaaaacc cctgaggacc ccccccatc ctcttctagg atgaggggaa gctggagccc 1560
caactttgat cctccattgg agtggcccaa atctttccat ctagggcaag tcctgaaagc 1620
ccaaggcccc ctccccagtc tggccttgcc tccagcctgg agaagggcta acatcagctc 1680
attgtcaagg ccacccccac ccagaaacag aaccgtgtct ctgataaagg ttttgaagtg 1740
aataaagttt taaaaactaa aaaaaaaaaa aaaaaaaaaa aaaaaa 1786
```

<210> 132

<211> 974

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (165)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (853)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (963)
<223> n equals a,t,g, or c

<400> 132
ggcagctaac ctcctcatcc ccgctgtggg ttctagcctc tctgaagccc tggacttgat 60
cgagtcggac cctgatgctt ggtgtgacct gagtaaattt gacctccctg aggaaccatc 120
tgcagaggac agtatcaaca acagcctagt gcagctgcaa gcgtncacat cagcagcaag 180
tcctgccacc ccgccagcct tccgccctgg tgcccagtgt gaccgagtac cgcttgatg 240
gccacaccat ctacagacct agccggagca gccggggcga gctgatcccc atctcccca 300
gcactgaagt cgggggctct ggcattggca caccgccctc tgtgtcaag cggcagagga 360
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cctgtaacag cctcacgccc aagagcacac ctgttaagac cctgcccttc tcgccctccc 480
agtttctgaa cttctggaac aaacaggaca cattggagct ggagagcccc tcgctgacat 540
ccaccccagt gtgcagccag aagggtggtg tcaccacacc actgcaccgg gacaagacac 600
ccctgcacca gaaacatgct gcgtttgtaa cccagatca gaagtactcc atggacaaca 660
ctccccacac gccaaacccg ttcaagaacg ccctggagaa gtacggaccc ctgaagcccc 720
tgccacagac cccgcacctg gaggaggact tgaaggaggt gctgcgttct gaggctggca 780
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ggcggagccc atncaagaaa gtccggaagt ctctggctct tgacattgtg gatgaggatg 900
tgaagytgat gatgtccaca ytgcaccaakt ytttatcctt ggcgacaayt gcccttgca 960
aantttcca gcct 974

<210> 133
<211> 634
<212> DNA
<213> Homo sapiens

<400> 133
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cagtgcctt tccaggcctt aagagaagta aaacttagct gcagcgtcag gaggtggacc 180
ccagagtgtg agtggcacgc ttctctgtga acccgctcctc accatgtttg ccacatctgg 240
ggcagtgga cgggggaagc cttactctgt cagcgaatgt ggcaagagct tctgctacag 300
ctcagtgtg ctgcgacatg aacgagctca cggcggtgac ggccgcttcc gttgcctaga 360
atgcggtgag cgctgtgcac gggctgtgta cctccgagcg cacaggcgca cgcattgtgg 420
ccagaccctc tacatctgca gtgagtgcgg acaaagcttc cgccacagcg gccgtcttga 480
cctacacttg ggcgcacacc ggcagcgatg ccgcacttgc ccctgccgca cwtgcggcg 540
gcgcttccc cacttcccg cgctgtgtct acaccggcgc cgccagcatc tgccagagcg 600
gccccgscgy tgcccgctgt gcgycctcag gttt 634

<210> 134
<211> 1855
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1818)
<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1845)

<223> n equals a,t,g, or c

<400> 134

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```

<210> 135

<211> 917

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (913)

<223> n equals a,t,g, or c

<400> 135

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```

tggccgcccc agttgggggg cgagctcggt ggtgacgcgc ggccctcacg tgacccarag 120
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tgccctgagc tcggcgggct ggcattcggc ccggggaaaa gcggagcagg tctgagaggc 240
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```

<210> 136

<211> 1271

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1236)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1255)

<223> n equals a,t,g, or c

<400> 136

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atccgcgggc tggccaykc catccgcctg ctccctggaat acacagactc aagctaygag 180
gaaaagaagt acacgatggg ggacgctcct gattatgaca gaagccagtg gctgaatgaa 240
aaattcaagc tgggcctgga ctttcccaat ctgccctact tgattgatgg grctcacaag 300
atcacccaga gcaacgccat cctgcggtac attgcccga agcacaacct gtgcggggaa 360
tcagaaaagg agcagattcg cgaagacatt ttggagaacc agtttatgga cagccgtatg 420
cagctggcca aactctgcta tgaccagat tttgagaaac tgaaccaga atacctgcag 480
gcactccctg aaatgctgaa gctctactca cagtttcttg ggaagcagcc atggtttctt 540
ggggacaaga tcacctttgt ggatttcac gcttatgatg tccttgagag aaaccaagta 600
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tcagccccga gctgtccccg tgttgcatga aggagcagca ttgactggtt tacaggccct 1140

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gctcctgcag catggtcctt gccttaggcc tacctgatgg aagtaaagcc tcaaccacaa 1200
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ggttttaaat t 1271

<210> 137

<211> 2017

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (295)

<223> n equals a,t,g, or c

<400> 137

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ttgaagtgga tgacaccttg aagaccaga tgaattcttt tctgctgtcc actgccagcc 120
aacaggagat tgctactcta gacaacaaga caatgactga tgtgggtggg aaccararga 180
rgagcgccga gctgagttct acttccagcc ctgggkcagg aggctgtgtg ccratacttc 240
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ccctgagctc ttcttcttc aataccatta aaaaaa 2017

<210> 138

<211> 937
<212> DNA
<213> Homo sapiens

<400> 138
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gagaggggaag aaggggaggt tggggggctc ctcccttca gaactgaag tttctccac 720
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<210> 139
<211> 2759
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (171)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1654)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2743)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2744)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2746)
<223> n equals a,t,g, or c

<400> 139

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<210> 140

<211> 1241

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (317)

<223> n equals a,t,g, or c

<400> 140

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ggggaaggag tggcacaagt tctgcctcaa gtgcgagcgc tgcagcaaga cgctgacgcc 180
cgggggccac gccgagcatg acgggaagcc gttctgccac aagccgtgct acgccaccct 240
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cctgcctgca agcccagggc gagtattgga ggaggggcag ccacgggcag agcaccatgc 840
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tcctccggga tccctgcct ggtgcccaca ctgctcgca agcgctcgcc accctcacgt 1140
ggctcacctg ctgttgagcc ttgtgctgtc aataaacggt ttgaggattg caaaaaaaaa 1200
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa g 1241
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<210> 141

<211> 3405

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1569)

<223> n equals a,t,g, or c

<400> 141

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tttgtcacgt gtgtccggca gccagaattc cgagccgtgc taggagaagt ggttctatac 120
tcaggagcca ggctctctc tcatcagcca ggccccgagg ctccctgccct cccaaagaca 180
gtgctcagc tcaagaaaga ggcaaaagaa cgggagaagc tagagaaatt ccaacagaag 240
cagaagatcc aacagcagca gccacctyca ggggagaaga aaccaaacc agagaagagg 300
gagaaacggg rtyctgggt cattamctwt gacytcccaa ccccamccgg ggaaaagaaa 360
gatgtcagtg gccccatgcc cgactcctac agccctcggt atgtggaggc tgcctgttac 420
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gtggtgggaga agaagctatg gcgtgagmag ggactgagcc ggcaccagct gggccgcgag 720
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<211> 2268

<212> DNA
<213> Homo sapiens

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<221> misc feature
<222> (2169)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2196)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2232)
<223> n equals a,t,g, or c

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tgtagcaaaa agttgattag cttaccaaga ttattaatag caatgtatgt gttataatac 2160
aacttagtna cattaagacc tacgaaaact catcnggct gtaggatagt aataaaggaa 2220
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<210> 143

<211> 1757

<212> DNA

<213> Homo sapiens

<400> 143

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attttcacac acagtgtgta agatgctgca agaccaaata atagctcata aaatcaggtc 180
ctgagatagt taccataaaa gaggaatcct ttgagtgtat gccattggtg agccgatgag 240
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<210> 144

<211> 1062

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (52)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1056)

<223> n equals a,t,g, or c

<400> 144

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gacaaccatt tccaagtact tctcagaacg tggggatgct gtggccaagg cctccaagga 780
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaanaaa aa 1062
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<210> 145

<211> 1030

<212> DNA

<213> Homo sapiens

<400> 145

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aggcctgggg ccaggacgct tgtctgccat gcacggactg atcatgggag gcctgggaagt 540
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aaaaaaaaaa

1030

<210> 146

<211> 814

<212> DNA

<213> Homo sapiens

<400> 146

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<210> 147

<211> 2678

<212> DNA

<213> Homo sapiens

<400> 147

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cgtgttaaga agcaacttca ggcattaagt tcagaattag cccaagccag agatgaaacc 180
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<210> 148

<211> 1028

<212> DNA

<213> Homo sapiens

<400> 148

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tgtataatth aaggaaggta aagttagggg actagaagac tctaaattgg cttctacaga 900
tcaataatth aaatgtaact agttgggatt ttatagttaa aattatattt gtgtatataa 960
cataactaat ctgtaaattg taataaatat atttgcaatt attaaatgtt aagtgatatt 1020
ttggttca 1028

```

<210> 149

<211> 1425

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (647)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1359)

<223> n equals a,t,g, or c

<400> 149

```
gcgtctccgg aagtggaggc gggagcggca cggcagccac tgcttggggt agcgggaggg 60
cagactctgg ggcgcaactcc cgggccggtc atgaacgggc cggcggacgg cgaagtggac 120
tacaacaaaa aataccggaa tctgaagcgg aagctcaagt tcctcatcta cgagcacgag 180
tgcttccagg aggagctgag gaaagcggca aggaaattac tgaaggtgtc ccgggacaag 240
agtttccctc tagaccgact tctgcagtac gagaacgtgg atgaagactc ttcggactca 300
gatgccactg catcatcaga taacagcgag acggaggggga caccacaagt gtctgacaca 360
ccggccccct agaggaagag aagccctccg ctggggggcg cccctctccc ctccagcctc 420
tccctgcctc cttcaacagg gtttccccct caggcctccg gggctccccct ccataacctg 480
agctcgctgg cctcctcccg ctacccccca ttcccttctg actacctggc cctgcagctg 540
cccgasccca gtcccttrag gccaagcgg gagaaacggc cccgmctgcc ccggaactc 600
aagatggcgg tgggaccccc cgaytgccct gtgggagggc cgctganctt ccctggccgg 660
ggtytgggg stggggtcgg gamaaccctg amccccctc caccacctaa gatgcccccc 720
cccacgatcc tgagcacggt ccctcggcag atgttcagcg atgcaggtag cggggacgat 780
gccttggtat gagacgatga cctggtgatc gacatcccgg agtgaccgtg acatcacgcc 840
atgcccacca cggccccgcc cggcgccctc cccgtgccag cacacacgag tccagcttcc 900
tcggaggtgt ttattgatgc ccagctgccg tgctccggcc actgacacaa ccagaaaagg 960
cgtaaacaatg cacgggtgtc cccaggagg gtgcaggggc cctgccttca aaccccgggc 1020
ccctccaggg gacagttatt taaacgagtg gccgggagca tctgccacct gctggggagg 1080
cagagaccct gcaatggcca cctctttaa agggcagctg tacagggcta ggttttttca 1140
atgaagtttc tgtattaaag gagtggctct gggtttgttt tttgtccttt ttttttgaga 1200
cattctcctc ctctgaacct cccctaattc gacctcctcc ctgttggggg agagggacgg 1260
ggcagcgtgg agaggcagga gtgaggagcg cgggggcctg gggccgggct ctgagcactg 1320
cccggtgtg cagatgatgg ggggtttgca tatttgcang ggactagcga gtcaggcagg 1380
aggtttgcat atgtgaatat agaactccgc agcccctcat gagca 1425
```

<210> 150

<211> 780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (285)

<223> n equals a,t,g, or c

<400> 150

```
gctgcgagaa gacgacagaa ggggagagcc aatggaaagg ggctgccgcg cggccgtaaa 60
```

```

gagttttag agcagttcgg gtgcggtacg ttgcattccg gtaccggacg ccgagagcgg 120
tttgtctccg tctctggagt tgtaggcgag aggtgatcat gtccggtcgc gggaaacagg 180
gcggcaaaagt gcgagcaaag gccaaatccc gctcctcccg cgcgggcctg cagttcccgg 240
tgggccgagt gcacagactg ctgcgcaaag ggaactacgc ggasnagtgg gcgccggggc 300
gccggtgtac ctggcgggcg tgttgagta ccttacggcg gagatcctgg agctggctgg 360
caacgcccg cgtagacaaca agaagaccag gataattccc cgccacctgc agctcgccat 420
ccgcaacgac gaggagttaa acaagctgct gggcaaagt accatcgctc agggcgggcg 480
cctgcccac atccaggccg tgctgctgcc caagaagacg gagagtcaga agacgaagag 540
caaatgaccc tgacgccgcc ctgaggagc tggtccsc agcaaaggcc cttttcatgg 600
tcgtcccga atgcttttga atgtgctgga tgcattggag ggccggtgac atctagcggg 660
gaggtggcg gcgaggggtcc cggcgggagc caataaaagt ggtgaaaatc gtaaaaaaaa 720
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780

```

<210> 151

<211> 1066

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1061)

<223> n equals a,t,g, or c

<400> 151

```

ggacccgccca tggcgcgga gaaggtgct cgcgggctga tcgcggagct ggcccgcgc 60
gtgcgcgccc tgcgggagca actgaacagg ccgcgcgact cccagctcta cgcggtggac 120
tacgagacct tgacgcggcc gttctctgga cgccggctgc cggtcggggc ctgggcccga 180
gtgcgcgccc agagccgcct cttgcagctg ctgcggccgc tcccgtctct cggcctgggc 240
cgctgtgtca cgcgcaagtc ctggctgtgg cagcacgacg agccgtgcta ctggcgctc 300
acgcgggtgc ggcccgacta cagggcgag aacttgacc acgggaaggc ctggggcatc 360
ctgaccttca aagacgcctc ttttcttca tcagggaaga ctgagagcga aggcgcggga 420
gatcgaacac gtcattgtacc atgactggcg gctggtgccc aagcacgagg aggagccct 480
caccgcgttc acgcggcgcc cggaagacag cctggcctcc gtgccgtacc cgcctctcct 540
ccgggccatg attatcgag aacgacagaa aaatggagac acaagcaccg aggagcccat 600
gctgaatgtg cagaggatac gcatggaacc ctgggattac cctgcaaaac aggaagacaa 660
aggaagggcc aagggcaccc ccgtctagaa tgccagaacc agcgggtggc cttaggggct 720
gtgaggcagt ggggacctta ttgatgaaag aaaccgtctt tgcgttacac ccgagtctgc 780
ctctcggagc agggagctca ccttcgcga cgtgttctga ggtctgcat cttagggggg 840
agggctgggg caaatcgcca cctgtgcctt tcctctggcc ctgctgcccc cacaccaac 900
tccgagggcc cagctgggg aaagcgggaa gcgctcgctc cctttcccc attagtgtc 960
tctctgcctg gatcccgcca gaagctatga aagggaataa agagaaaaga artamaaaaa 1020
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa nccctt 1066

```

<210> 152

<211> 1649

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1543)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1579)

<223> n equals a,t,g, or c

<400> 152

```
accccggtc tccaaggagg tgtgacatca tcatcatctc tggccggaaa gaaaagtgtg 60
aggctgccaa ggaagctctg gaggcatttg ttctgtcac cattgaagta gaggtgccct 120
ttgaccttca ccgttacgtt attgggcaga aaggaagtgg gatccgcaag atgatggatg 180
agtttgaggt gaacatacat gtcccgccac ctgagctgca gtctgacatc atcgccatca 240
cgggcctcgc tgcaaatattg gaccgggcca aggtctggact gctggagcgt gtgaaggagc 300
tacaggccga gcaggaggac cgggctttaa ggagttttaa gctgagtgtc actgtagacc 360
ccaaatacca tcccaagatt atcggggaaa agggggcagt aattaccaa atccggttgg 420
agcatgacgt gaacatccag ttctctgata aggacgatgg gaaccagccc caggaccaa 480
ttaccatcac agggtagcaa aagaacacag aagctgccag ggatgctata ctgagaattg 540
tgggtgaact tgagcagatg gtttctgagg acgtcccgtt ggaccaccgc gttcacgccc 600
gcatcattgg tgcccgcggc aaagccattc gcaaaatcat ggacgaattc aaggtggaca 660
ttcgttcccc acagagcggg gcccagacc ccaactgcgt cactgtgacg gggctcccag 720
agaatgtgga ggaagccatc gaccacatcc tcaatctgga ggaggaatac ctgctgacg 780
tggtggacag tgaggcgctg caggtataca tgaaccccc agcacacgaa gaggccaagg 840
caccttccag aggttttgtg gtgcgggacg caccctggac cgccagcagc agtgagaagg 900
ctcctgacat gagcagctct gaggaatttc ccagcttttg ggctcaggtg gctcccaaga 960
ccctcccttg gggcccaaaa cgataatgat caaaaagaac agaaccctct ccagcctgct 1020
gacccaaacc caaccacaca atggtttgtc tcaatctgae ccagcggtctg gaccctccgt 1080
aaattgttga cgctcttccc ccttcccag gtccgcagg agcctagcgc ctggctgtgt 1140
gtgcggccgc tcctccaggc ctggccgtgc ccgctcagga cctgctccac tgtttaacac 1200
taaaccaagg tcatgagcat tctgtctaag ataacagact ccagctcctg gtccaccg 1260
catgtcagtc agcactctgg ccttcatcac gagagctccg cagccgtggc taggattcca 1320
cttctgtgt catgacctca ggaataaaac gtccttgact ttataaaagc caaacgtttg 1380
ccctcttctt tccccacctc cctcctgcca gtttcccttg gtccagacag tcctgtttgt 1440
ggagtgaat cagctcctc cagctgccag agcgctcag cacaggtgtc aggtgcaag 1500
gaagacctgg caatggacag caggaggcag gttcctggag ctnggggggtg acctgagagg 1560
cagaggggtg cgggttctna ggcagtctg attttacctg ccgtgggggtc tgaaarcacc 1620
aagggtccct gacctacct cactgcca 1649
```

<210> 153

<211> 660

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (35)

<223> n equals a,t,g, or c

<400> 153

```
ccggaaattc ccgggtcgac ccacgcgkcc gcggnagwgc tcacacgtgt gtcacctgcc 60
ctgctcctgg ccccttgccc ggccgggctg ttcttgccca tgggtcgctc ccgccggaca 120
ggcgcgcacc gagcgcactc tctagcccgg cagatgaagg cgaacggcgg cggccggact 180
```

tggatgagat tcaccgcgag ctgcggcctc agggatccgc acgacccag cccgacccaa 240
acgccgagtt cgaccccgac ctgccagggg gcggtctgca ccgctgtctg gcctgcgcga 300
ggtacttcat cgattccacc aacctgaaga cccacttccg atccaaagac cacaagaaaa 360
ggctgaagca gctgagcgtc gagccctaca gtcaggaaga ggcggagagg gcagcgggta 420
tgggatccta tgtgcccccc aggcggctgg cagtgccac ggaagtgtcc actgagggtcc 480
ctgagatgga tacctctacc tgacatggc tgaagatgca ggcagagga attgcccattg 540
gacagtgacg caaggactag gctgggaggg agcgtgccaa ccccttttgc ctctgggttt 600
ggggagcgga ggcctcttc ttggtgccct gcccacaata aaggaactgg acaaagagaa 660

<210> 154

<211> 605

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (449)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (574)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (578)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (583)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (587)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (596)

<223> n equals a,t,g, or c

<400> 154

ggcagagctc caccttccat ccggcgccgg ctttcggcgc gacggtcgcc gcgttccatc 60
gtcgcgcggc ccttcgggcy cccgagcccg caatgtcggg cccaacgga gacctgggga 120
tgccgggtgga ggcgggagcg gaaggcgagg aggacggctt cggggaagca gaatacgtg 180
ccatcaactc catgctggac cagatcaact cctgtctgga ccacctggag gagaagaatg 240
accacctcca cgccgcctc caggagctgc tggagtccaa ccggcagaca cgcctggagt 300
tccagcagca gctcggggag gccccagtg atgccagccc ctaggctcca agagcccca 360

```

accgggaccc aaccctgcct ccctgggcta ggctctggcc tgggcactca mcccctggct 420
tagacamctt ctcaagggct ggccttcang gaccctgggt gggctctgcct gcctgggcca 480
accttcctgc ctgggscctc ccttggctam ctgggscagc cccacccaac tggcatgccc 540
tcctgggggc caaagaatgg ggcctgcaac ccancantt gcntgcncaa cccaanttcc 600
tggggg                                           605

```

<210> 155

<211> 695

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (173)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (499)

<223> n equals a,t,g, or c

<400> 155

```

gaaccctaga aaaaaggatg cagtactaaa gtgtcattca ttcaaagcca ctctcttttt 60
gggtattccac ccattttcca gacggtgaca ctgaggctca ggaagcagta gggacttgca 120
caaagccctt tgggaagcag gctgggaaac agtggaggga ggggtgtccat tanccccaag 180
gagacacagg atctgggctc tktytttsgc cttcctccca gaatacgtg ccatcaactc 240
catgctggac cagatcaact cctgtytgga ccacctggag gagaagaatg accacctcca 300
cgcccgccct caggagctgc tggagtccaa ccggcagaca cgcctggagt tccagcagca 360
gctcggggag gccccagtg atgccagccc ctaggctcca agagccccc accgggaccc 420
aaccctgcct ccctgggcta ggctctggcc tgggcactca ccccctggct tagacacctt 480
ctcaagggct ggccttcang gaccctgggt gggctctgcct gcytgggcca cccttcctgc 540
ctgggrcctc cccttgkkcc tactggggcc agccccacc acctggcatg ccctcctggg 600
gccaagagtg ggcctgcaam ccaccattg setgccaac caattcctgg gcgytcccca 660
wtytgcaccag gcttgaatgt tcacatgaaa tgggt                                           695

```

<210> 156

<211> 780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (289)

<223> n equals a,t,g, or c

<400> 156

```

cggtgggctc gcgttgaggc tgcggtcag gagggagcag gagctggatc cggttcccg 60
aaggagctgg tgagcaggct gctgcacctg cacttcaagg atgacaagac caaagtgagc 120
ggggacgcgc tgcagctcat ggtggagttg ctgaaggtct tcgttggtga agcagcagtc 180
cgcgcgctgc ggcaggccca ggcagaagac gcgtccgtg tggacgtgga ccagctggag 240
aaggtgcttc gcagctgctc tggacttcta gggatctcag ccgtggckna ggccaccccc 300

```

118

```

agaggagccc ctggtccaca gaagcaggcc ttgtgtttcc agcggcctct gataagaggc 360
aggggaaggam ctgaaggatt tggarttgat tcaaacaaga tctctgggag tctccagcct 420
gtgcagaagg ggcaggactg cagtgcactg cgggccttgg agtgtccagt ggggacactg 480
gtgtgggaag gggcagcacc tggggagtcc ctgcctctcc tccctgggac aatagtgtgc 540
atgccacccg gggtcctaca ggcagggtgct gggaaggcc tggccagcag gtagcctgtg 600
tgtttgacaa acagcagctg gcagcgtgc ctctgccc cattcctgcc acccgacatc 660
aaagctggcg tgtgacctt ccagccatgc gatattcccc ttggaagatg cttccccagg 720
ctataaattt gttctcacia agcaacatca ataatcaaa actgtctcty ccaaaaaaaa 780

```

<210> 157

<211> 1127

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1113)

<223> n equals a,t,g, or c

<400> 157

```

aacttcagt ccctcactgt agaatttaaa agccttactg ttgattgccc atggtggact 60
tgatggagaa attaaatata ttccattatg ctttcaaaaa tactgtatat gtttcagcaa 120
gtttggggaa tgggagagga caaaaaaag ttacatttaa tctatgcatt tttgccaagc 180
catattgagt tattttacta ctagagacat taggaaacta actgtacaaa agaaccaagt 240
ttaaaagcat tttgtggggt acatcatttc tataattgta taatgtattt ctttgtgggt 300
ttaaatgata aagacattaa gttaacaaac atataagaaa tgtatgcaat gtttgaaatg 360
taaattatc ttagaacact ttcaatggg gttgcattgt ctttttagtg ccttaatttg 420
agataattat ttactgcca tgagtaagta tagaaatttc aaaaaatgta ttttcaaaaa 480
attatgtgtg tcagtgaagt ttccattgat aattgggtta attttaaata ttttagaggtt 540
tgttggactt tcataaattg agtacaatct ttgcatcaaa ctacctgcta caataatgac 600
tttataaaac tgcaaaaaat gtagaagggt gcaccaacat aaaaaggaaa tatggcaata 660
catccatgat gttttccagt taacatagga attaccagat aaatactggt aaactcctgt 720
ccagtaacaa gagttgattc atatggacag tatgatttat tgtttatttt ttaacccaaa 780
tacctcctca gtaatttata atggccttgc agtaatgtgt atcagataag aagcactgga 840
aaaccgatcg tctctaggat gatatgcag tttcaagtgg tattgaaagc cgcactgatg 900
gatatgtaat aataaacata tctgttatta atataactaat gactctgtgc tcattttaat 960
agaaataaaa gtaatttatg gatgggtatc ttttaattttt actgcaatgt gttttctcat 1020
ggctgaaatg aatggaaaac atacttyaat tagtctctga ttgtatataa atgtttgtga 1080
aattccatgg ttagattaaa gtgtrttggg aanaattctc catggggg 1127

```

<210> 158

<211> 1282

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (120)

<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (205)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (207)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (236)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (732)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1279)
<223> n equals a,t,g, or c

<400> 158
tgctctacaa atagtaaaaa taaaaaataa aaaaagtagc tgggcgtggt ggtgtgcacc 60
tgtgggtccca gctgcttggg atgctgaggt ggaaggatct cttaaaccce ggagggtggn 120
aggctgcagt gaacttgcca ttgcaccact ggcactccag tctgggggac agagtgcagac 180
cccatctcaa aaaagtgttt aattnantat acttgtagt ggtctatttg catttnaaaa 240
ctgctttcta gaattaggat agctccctta ggtttaatgt tttggtgagc aggaatatca 300
gttacccttc cagatcttaa ttctagtttt tttatcactt tttcatgagg tgatctcatc 360
ctcatctcct agcatgtctg gcaattttga tttctgaact ctgtgctacc tcagaggcca 420
gcttccttag ggaaaaatca gtgctgaaat aaagttatat ttccttttct gctctaaata 480
tatagtgggg gaataagaga aatgaagagg aattcctgag aacgtaatta ctagaaactc 540
ccctctccca cgtaatgtct ctacacacac atggaccctt attcccccaa tttgcgaccc 600
cccacccac cccacaacag gtggtgatct ttgtgaagtc tgtgcagcgg tgcattgcct 660
tggcccagct actagtggag cagaacttcc cagccattgc catccaccgt gggatgcccc 720
aggaggagag gntttaaaga ttttcaacga cgaattcttg tggctaccaa cctatttggc 780
cgaggcatgg acatcgagcg ggtgaacatt gcttttaatt atgacatgcc tgaggattct 840
gacacctacc tgcacgggt ggccagagca ggccggtttg gcaccaaggg cttggctatc 900
acatttgtgt ccgatgagaa tgatgccaa atcctcaatg atgtgcagga tcgctttgag 960
gtcaatatta gtgagctgcc tgatgagata gacatctcct cctacattga acagacacgg 1020
tagaagactc gccattttg gaatgtgacc gtctgtcctt caggagagga caccagggtg 1080
gggggtgaagg agacactact gccccaccc ctgacagccc ccaccccatg gcttccatct 1140
tttgcacac caccactcct gaaccccat ttctgatttg tcagaatttt tttttaacaa 1200
aactaaaaat gaaacacatg tgtctgtggt atctaaaaaa aaaaaaaaaa aaawwggggg 1260
ggsgcccgta cccattggnc ct 1282

<210> 159
<211> 1505
<212> DNA

<213> Homo sapiens

<400> 159

```
ttacatgttg cagaagctaa ttgaagagac agataggttt gtagtggtca cagaagagga 60
atcaggcatg agtgaccagt tgtgtggcat tgctgcctgc cagacggatg acatatacaa 120
ccgaaactgc cttattgaat tggtaaacct gtcagatggt tcttcgtgga gcagagacak 180
aaggctgtgt catttgtgtca gctgccaaag cccaactgct gcagtgccag caccatccag 240
cctggtatgg tgatacattg aagcaaaaaga catcctggac ttgcctcttg gatggcatgc 300
agtactttgc caccactgaa agcagcccca cagagcagga tggccgacag ctctgggttag 360
aggtgaagaa tatcgaggag caccggcagc gtagtctgga ctctgtgcag gagctgatgg 420
agagtgggca ggcagtgggc ggcattggtta ccacaaccac agattggaac cagccagctg 480
aggcacagca agcccagcaa gtccagcgga tcatttcgcg ttgcaactgc cgaatgtact 540
atattagtta cagccatgac attgatcctg aactagcaac tcagattaag ccacctgaag 600
ttcttgagaa ccaggaaaag gaagatctcc taaagaagca ggaaggggct gtggatacct 660
tcaccttat ccaccatgag ctggaaatth ccaccaaccc agctcagtat gccatgatcc 720
tggaattgt caacaacctg ctgctccatg tagaacctaa gcggaaggaa catagtgaga 780
agaagcaacg ggtcagggtc cagcttgaga tctctagcaa tccagaggag caacgcagca 840
gcatactgca tttgcaggag gctgtgcggc agcatgtggc ccaaatacga cagctggaga 900
agcagatgta ttctatcatg aagtctttgc aggatgacag caagaatgag aatctgcttg 960
acctgaacca gaagcttcag ttgcagctaa accaggagaa ggccaacctg cagctggaaa 1020
gtgaagaact gaatatcctc atcagggtgt ttaaggattt ccaactgcag cgggctaaca 1080
agatggagct gcgaaagcac aagaagatgt gagtgtggtc cgtcgcactg agttttactt 1140
tgctcaggca cggtgggcgc tgacagagga agatggacag ctgggaattg ctgaattaga 1200
actgcagagg ttctctaca gcaagggtgaa taagtctgat gacacagcag aacatcttct 1260
ggagttgggc tggtttacca tgaacaacct cctcccaaat gctgtctata aggtagtact 1320
gcggccccag agtcctgcc agtctgggcg acagctagct ctccgcctct tcagcaaaag 1380
tcggccccct gttgggggta tctctgttaa ggagcatttt gaggtaaatg tgggtgctctc 1440
accatccagc tgacacacca ttcttcaca gatgatgggc ttttctttcc tggccgaagt 1500
gtgga 1505
```

<210> 160

<211> 736

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (718)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (723)

<223> n equals a,t,g, or c

<400> 160

```
aggcacgagg gacacttggg gtctggacgc aacggcggcg ggagcatgaa cgcccccca 60
gccttcgagt cgttcttgct cttcaggggc gagaagatca ccattaacaa ggacaccaag 120
gtacccaatg cctgtttatt caccatcaac aaagaagacc acacactggg aaacatcatt 180
aaatcacgtg cctgtctccc cttcgccctc tgccgtgatt gtcagtttcc tgaggcctcc 240
ccagccacgc ttctgtaca gcctgcagaa ctgtgagtca attaaacctc ttttcttcat 300
```

```

aaattaccca gtttctcata gttctttata gcagtgtgaa aacagactaa tggacccttc 360
tggttgaagg aatgcagcca ttctgcttgt ttgactatgt cctttctatt catctctatt 420
tcctgggagg tgtttatcca agtgcaatag gaggtattgg tgaccgcaca gtcccctcag 480
tgttctgcta gtaaatagtt gaaggttgat cattgatctt ctgcgttttc agtctggcat 540
ggaaaagccc ctgtgcaact ggtaaagata tcaataagca cctgggtgggt ggcgggggta 600
gtccaggctt gtcttgcaac tgtatgttct cttcagaccc ctccctggcg atgccagatt 660
cactgggctg gcagattctg ccccccccaa aaaaaaaaaa aaaatattaa taataaanaa 720
aanagactcc caggga                                     736

```

<210> 161

<211> 995

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (59)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (889)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (899)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (928)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (933)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (938)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (974)

<223> n equals a,t,g, or c

<400> 161

```

gggtcgaccc acgcgtccgg gcggcctcgg cagcgggtgt ctcgcgcttg cgaasgggnc 60

```

```

tccggctcgg ctgcgggga ctgtgcacga ggttggcgac gcgccccgcc gggccccaga 120
tcaggccgca gagatcgga gccgcgggag cactaaggcg caagggccac agcagcagcc 180
gggctcagag ggtcccagct atgccaaaa agttgcgctc tggcttgctg ggctgcttgg 240
agctggtggg actgtgagcg tcgtctatat ctttgaaac aaccggtgg acgaaaatgg 300
tgccaagatt cctgatgagt tcgacaatga tccaattctg gtacagcagt tgcgccggac 360
atacaaatat ttcaaagatt atagacagat gatcatcgag cccaccagcc cttgccttct 420
cccagaccct ctgcaggaac cgtactacca gccaccctac acgctcgttt tggagctcac 480
cggcgctcctc ttgcatcctg agtggctcgt ggccactggc tggaggttta agaagcgccc 540
aggcatcgag accttgttcc agcagcttgc ccctttatat gaaattgtca tctttacgct 600
agagactggc atgactcgtt ttccactcat tgatagtgtg gaccccatg gcttcatctc 660
ctaccgccta ttccgggacg ccacaagata catggatgga caccatgtaa aggatatttc 720
atgtctgaat cgggacccag ctcgagtagt agttgtggac tgcaagaagg aagccttccg 780
cctgcagccc tataacggcg ttgccctgcg gccctgggac ggcaactctg atgaccgggt 840
cttggttgat ctgtctgcct tcctcaagac cattgcactg aatggtgtng gaggacgtng 900
cgaaccgtgc tgggagcatt atgccctngg ganggatnga ccccgctggg cggtttttyc 960
aaacagcggc aaancgggct tagaagcagg gagga 995

```

<210> 162

<211> 1125

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (972)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1023)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1077)

<223> n equals a,t,g, or c

<400> 162

```

gccctagtagt ggtccggaat tcccgggtcg acccacgcgt ccgcccacgc gtccgcgctg 60
gtgttgccggc gctggcgaca gtcggggttg cgagcggccc ggggcccggg cggccagggc 120
cgctgcagga cgagaccctg ggtgtggcgt ccgtgccctc gcagtggagg gccgtccagg 180
gcatccgcgg ggagacgaaa agttgccaga cggccagcat tgccactgcc agtgcacccg 240
cccaggccag gaatcatgtg gacgcccagg tgacagcaga gggcccgctg cctgtcagcg 300
tgacgcccc gtcccagtay gacataccca ggctcgcagc ctttcttcgg agagtggagg 360
ccatgggtcat ccgagagctg aacaagaatt ggcagagcca cgcgtttgat ggcttcgagg 420
tgaactggac cgagcagcag cagatggtgt cttgtctgta taccctgggc taccgccag 480
cccaagcgca gggctgcgtg gtgaccagca tctcctggaa ctccactggc tctgtggttg 540
cctgtgccta cggccggctg gacctgggg actggagcac gcttaagtcc ttcgtgtgtg 600
cctggaacct ggaccggcga gacctgcgc cccagcaacc gtcggccgtg gtggaggtcc 660
ccagcgctgt cctgtgtctg gccttcacc ccacgcagcc ctccamgtc gcaggaggcg 720
tgtacagtgg tgagggtgtg gtgtgggacc tgagccgtct tgaggaccgc ctgctgtggc 780

```

```

gcacaggcct gacggatgac acccacacag accctgtgtc ccagggtggtg tggctgcccc 840
agcctgggca cagccamcgg ttycaggtgc tkagtgtggc cacygacggg aaggtgctac 900
tctggcargg catcggggta rgccagctgc agttcacaga rggcttcgcc tggttcatkc 960
agcagctgcc anggagcacc aagctcaaga agcatccccg cgggagaccg aggtggggcg 1020
canggcaggc tttcttccag tttgacctca ggttttcatt ttggcaggaa gcggttnccg 1080
ttcaattttc ctggcattgg agagcagcct taaggggtgc ccatt 1125

```

<210> 163

<211> 423

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (390)

<223> n equals a,t,g, or c

<400> 163

```

gggtcgaccc acgcgtccga gatggcggtt cgcagcaaga ggccggagca cggcgggccc 60
ccggagctgt tttatgacaa gaatgaagcc cggaaatacg tgcgcaactc acggatgatt 120
gatgtccaga ccaaagtggc tgggcgagct ttggagctcc tttgtctgcc ggaggtcagc 180
cctgttacct cttggatatt ggctgtggtt ctgggctgag tggagattat ctctcggatg 240
aagggcacta ctgggtagc atcgacatca gccctgccat gctggatgcg gccttggacc 300
gagacactga gggagacctg cttctggggg acatgggcca gggcatcccc ttcaaaccag 360
kttcattgat ggatgtatca gcattctgcn aatcagtggc tctgtaatgc aaaccaagaa 420
gtc 423

```

<210> 164

<211> 1642

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1614)

<223> n equals a,t,g, or c

<400> 164

```

acccacgcgt cggcggtctg gcggagcaga acggattgca gggtcagcca tgtcatctga 60
gcctccccca ccaccacagc cccccacca tcaagcttca gtcgggctgc tggacacccc 120
tcggagccgt gagcgctcac catccctctc gcgsggcaac gtggtcccaa gccactgcc 180
cactcgccgg acgaggacct tctcggcgac ggtgcgggct tcacagggcc ccgtctacaa 240
aggagtctgc aaatgcttct gccggtccaa gggccatggc ttcattacc cagctgatgg 300
cggccccgac atcttctctg acatctctga tgtggaagg gagtatgtcc cagtgaagg 360
cgacgaggtc acctataaaa tgtgtccat cccacccaag aatgagaagc tgcaggccgt 420
ggaggtcgtc atcactcacc tggcaccagg caccaagcat gagacctgg ctggacatgt 480
catcagctcc taggagatgg tggaaagcacc cettgtctctg tgcttgagg agactttgcg 540
gggaggaggc agcagacact ggagatgaca ttcttcaca cgagacggg cttcagccgg 600
gcatggtccc tctcaagtat ctcttgagg aaggggtatg gggggcagg gtggggtgtg 660
gggtgttccc ggccatcagc acagcctatg accattgcaa caacctctca ccattctgaag 720
agcattaaaa gcatttaaaa aggaragggt cccactgggtg gctgagtggg ggttccaacc 780

```

```

ccatcccagg gagtggatca aggggtggtat ttctccagct gctcagacac atgggctcaa 840
cccacagaat ccctcttcct cctggagctg gaggccccag attcccagat ctggccccct 900
ggcagcctga cagggacctt gcgtgacttc tccaaggcaa atttccacct aagtgccctt 960
tgcgcctctc ctggggcctg ggcaaagcag ttttctaatt cttggcttgg ttggttctag 1020
gggagctggc ttgaagtggg kggggaaagg cgggggtggc ggtcttttga ttggacggat 1080
gttgccctttt ggtgcctttg cagtgggagg cggcatagct gcctgtcttg ggaagacagt 1140
tctcccagca ctcccacccc tgggcacagc aggctggtac tgggaggctg aaccctctt 1200
agagcctgac cttttcatct gccttctggt tgtgtgacca tcaactcaaca gccatttcac 1260
agcccctgta attatggcgg cggggggctg ggggtggtgg ggtgggaagg gcttgtggag 1320
aggacacagt ctttgtttta aaactttgtc ccgatccatc cagaaaagag taggtagctt 1380
gcacccctgac agcctggcaa agtcaagaaa gttgaaggag aaacatacct ttggagaggg 1440
ggttttcttt aaaactagtg ttaagaaatg cttaggagatt ttttttttct tatttttcat 1500
aactaaagct ttcaccaga gccggctctg tttgcacttt gctgccgaca ttgcaaactt 1560
tttggcaggg tgggagactg agtctcattc tgcamccag gctggagtgc agtngcccga 1620
tctcagcttt actgcaacct ct 1642

```

<210> 165

<211> 1115

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (390)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (394)

<223> n equals a,t,g, or c

<400> 165

```

aggaatgccg agtactgcag gggctcccca gggagtatgt gaatgccagg cactgtttgc 60
cgtgccaccc tgagtgtcag cccacagaatg gctcagtgc ctgttttga cggaggctg 120
accagtgtgt ggctgtgcc catcaagtgg atggcgctgg agtccattct ccgccggcg 180
ttcaccaccc agagtgatgt gtggagtatt ggtgtgactg tktgggagct gatgactttt 240
ggggccaaac cttacgatgg gatcccagcc cgggaggatc cctgacctgc tggaaaagg 300
ggagcggctg ccccagcccc ccatctgcac cattgatgtc tacatgatca tggtaaatg 360
ttggatgatt gactctgaat gtcggccaan atnccgggag ttggtgktg aattctccc 420
catggccagg gacccccagc gctttgtggt catccagaat gaggacttg gccagccag 480
tcccttgac agcaccttct accgctcact gctggaggac gatgacatgg gggacctggt 540
ggatgctgag gagtatctgg taccacagca gggcttcttc tgccagacc ctgccccgg 600
cgctgggggc atggtccacc acaggcaccg cagctcatct accaggagtg gcggtgggga 660
cctgacacta gggctggagc cykctgaaag aggaggcccc caggtctcca ctggcaccct 720
ccgaagggct ggctccgatg tatttratgg tgacctgga atgggggcag ccaaggggct 780
gcaaagcctc cccacacatg accccagccc tctacagcgg tacagtgagg accccacagt 840
acccctgccc tctragactg atggctacgt tgccccctg acctgcagcc cccagcctga 900
atatgtgaac cagccagatg ttcggcccc gccccctcg ccccgagagg gccctctgcc 960
tgctgcccga cctgctggtg ccactctgga aaggsccaag actctctccc caggaagaa 1020
tggggtcgtc aaagagtttt tgcttttgg ggtgccgtgg agaaccocga gtattgacac 1080
cccaggggag ggagcttgcc cttcagcccc acctt 1115

```

<210> 166
<211> 1066
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (10)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (739)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (968)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1023)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1025)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1042)
<223> n equals a,t,g, or c

<400> 166
gggcacgagn cacctgagcc ccttgtctcg caccggctcc caggagggca cctccatgga 60
gggctcccgc cccgctgccc ctgccagagc caggcaccct caagaccagt ctggtggeta 120
ctccaggcat tgacaagctg accgagaagt cccagggtgc agaggatggc accttgcggt 180
ccctggaacc tgagccccag cagagcttgg aggatggcag cccggctaag ggggagccca 240
gccaggcatg gagggagcag cggcgaccgt ccacctcatc agccagtggg cagtggagcc 300
caacgccaga gtgggtcctc tcctggaagt cgaagctgcc gctgcagacc atcatgaggc 360
tgctgcagggt gctggttccg cagtggagaa gatctgcac gacaagggcc tgacggatga 420
gtctgagatc ctgcggttcc tgcagcatgg caccctggtg gggctgctgc ccgtgcccc 480
ccccatcctc atccgcaagt accaggccaa ctcgggcact gccatgtggt tccgcaccta 540
catgtggggc gtcattctatc tgaggaatgt ggacccccct gtctggtacg acaccgacgt 600
gaagctgttt gagatacagc ggggtgtgagg atgaagccga cgaggggctc agtctagggg 660
aaggcagggc cttggtccct gaggttccc ccatccacca ttctgagctt taaattacca 720
cgatcagggc ctggaacang cagagtggcc ctgagtgtca tgccctagag acccctgtgg 780
ccaggacaat gtgaactggc tcagatcccc ctcaaccctc aggctggact cacaggagcc 840

126

ccatctctgg ggctatgccc caccagagac cactgcccc aacactcgga ctccctcttt 900
aagacctggg ytcagtgtg gcccctcagt gccaccact cctgtgttac ccagccccc 960
gaggcagnaa rccaatgggt cactgttgcc cctaaagggg ggtttttgaa ccaaggggga 1020
aancnacggg gcctgggtcc cntttggaaa ggttcccct gggaaa 1066

<210> 167

<211> 657

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (278)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (564)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (597)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (602)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (635)

<223> n equals a,t,g, or c

<400> 167

gtcgcgagcg ctgccgtcgg gaggcgctcc gaggttcgag gctgtgcccc gcgaccccg 60
cttcggcgct cggctcgcag gatggatccc gtaccgggga cagactcggc gccgctggct 120
ggcctggcct ggtcgtcggc ctctgcaccc ccgcgcggg gkttcagcgc gatctcctgc 180
accgtcgagg gggcaccgcc agctttggca agagcttcgc gcagaaatct ggctacttcc 240
tgtgccttag ttctctgggc agcctagaga acccganga gaacgtggtg gccgatatcc 300
agatcgtggt ggacaagagc cccctgccgc tgggcttctc ccccgctcgc gamcccatgg 360
attccaaggc ctctgtgtcc aagaagaaac gcatgtgtgt gaarctgttg cccctkggar 420
ccamggacac ggctgtgttt gatgtccggc tgagtgggaa gaccaagaca gtgcctggat 480
accttcgaat aggggacatg ggcggtttt ccatctggtg caagaaaggc caaggccccc 540
aggccagttg cccaagccc cgangtcctc agcccgggac atgcaagggc ttctctntgg 600
angcagccag ccagcccaag ttaagggcgg gcctncttgg aagccggaca agcgttc 657

<210> 168

<211> 1026

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1011)

<223> n equals a,t,g, or c

<400> 168

```

ggcacgagga gagatggagg ggcggcaggt gctggaggtc aagatgcagg tggagtacat 60
gtcattcagc gcacacgcgg acgccaaggg catcatgcag ctggtggggc aggagagacc 120
gkagagcgtg ctgctggtgc atggcgaggc caagaagatg gagttcctga agcagaagat 180
cgagcaggag ctccgggtca actgctacat gccggccaat ggcgagacgg tgacgctgcc 240
cacaagcccc agcatcccc taggcatctc gctggggctg ctgaagcggg agatggcgca 300
ggggctgctc cctgaggcca agaagcctcg gctcctgcac ggcaccctga tcatgaagga 360
cagcaacttc cggctggtgt cctcagagca agccctcaaa gagctgggtc tggctgagca 420
ccagctgcgc ttcacctgcc gcgtgcacct gcatgacaca cgcaaggagc aggagacggc 480
attgcgcgtc tacagccacc tcaagagcgt cctgaaggac cactgtgtgc agcacctccc 540
rgacggctct gtgactgtgg agtccgtcct cctccaggcc gccgcccctt ctgaggaccc 600
aggaccaag gtgctgctgg tctcctggac ctaccaggac gaggagctgg ggagcttctt 660
cacatctctg ctgaagaagg gcctccccc ggccccagc tgaggccggc aactcaccca 720
gccgccacct ctgccctctc ccagctggac agaccctggg cctgcacttc aggactgtgg 780
gtgccctggg tgaacagacc ctgcaggctc catccctggg gacagaggcc ttgtgtcacc 840
tgctgcccc ggagctgtt tgagctgaa gaaacaaact ggtctccagg ctgtcttgcc 900
tttattcctg gttagggcag gtggtcctag acagcagttt ccagtaaaag ctgaacaaaa 960
aaaaaaaaaa aaaaaattgg gggggggccc gttaccatt tggcctttag nggggggttt 1020
aaatta                                           1026

```

<210> 169

<211> 774

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (730)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (733)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (754)

<223> n equals a,t,g, or c

<400> 169

```

ggcataaaca tcgggtggtg ttcagatcct gctgccggca gctcgaggct aggatggctg 60
gagatgtgag ggcctttgtc tcatcacatc cgagcacagc tcagcaagat gctcttagct 120
agraaacaga tttatgtgt taatgttaaa aattttgcag ttatttatct tgtggatatt 180

```

```
acagaagtgc ctgacttcaa caaaatgtat gagttatacg atccatgtac tgtcatgttt 240
ttcttcagga acaagcacat catgattgac ttggggactg gcaacaacaa caagattaac 300
tggggccatgg aggacaagca ggagatggg gacatcatcg agacgggtga ccgcggggcc 360
cgcaaargcc gcggcctggt ggtgtccccc aaggactact ccaccaagta ccgctactga 420
ggcgccctca gtctgcgcgg ataaatgtcg tggagccctt tttgtatgga aacgttttaa 480
gctattttaa gcctttggaa aatacaggaa gctccagggc tggagcacct ctgagatgga 540
attgataaca tgggtcttaac tcaccgaaat aaacaagcac gtgggtgagag gagcaggcct 600
acttgtttgt tctcaggaaa cttaatgaat agattactga ttttcctagt caaagttaat 660
tcttaccctt ggagtaaaac gaagggtgtt atcctgtgag cctgtgcgtt ttgcatactg 720
ggttgggttn ctngggcttc ggtgacagca tatnccgcga gctgggcttt aaca 774
```

<210> 170

<211> 402

<212> DNA

<213> Homo sapiens

<400> 170

```
ggcacgagcg gcggtggggc ggacagccgg ggtgcgcact tgggcccccc tggccatggc 60
ggcgaagggt gacctgagca cctccaccga ctggaaggag gcgaaatcct ttctgaaggg 120
cctgagtgc aagcagcggg aggaacatta cttctgcaag gactttgtca ggctgaagaa 180
gatcccgaca tggaaggaga tggcgaaagg ggtggctgtg aagggtggag agcccaggta 240
taaaaaggac aagcagctca atgagaaaat ctccctgctc cgcagcgaca tcaccaagct 300
ggaggtggac gccatcgtca acgcccga cagctccccg ccccgagga gcctaattaa 360
agatcttcgt tgtggcaaaa aaaaaaaaaa aaaaaaaaaa aa 402
```

<210> 171

<211> 796

<212> DNA

<213> Homo sapiens

<400> 171

```
aggcatcggg gacagccgct gcggcagact cgagccagct caagcccgca gctcgcaggg 60
agatccagct ccgtccctgcc tgcagcagcc caaccctgca caccaccat ggatgtyttc 120
aagaagggtt tctccatcgc caaggagggc gtggtgggtg cgggtgaaaa gaccaagcag 180
ggggtgacgg aagcagctga gaagaccaag gaggggttca tgtatgtggg agccaagacc 240
aaggagaatg ttgtacagag cgtgacctca gtggccgaga agaccaagga gcaggccaac 300
gccgtgagcg aggtgtggt gagcagcgtc aacactgtgg ccaccaagac cgtggaggag 360
gcggagaaca tcgcggtcac ctccggggtg gtgcgcaagg aggacttgag gccatctgcc 420
ccccaacagg aggtgtaggc atccaaagag aaagaggaag tggcagagga ggcccagagt 480
gggggagact agagggttac aggccagcgt ggatgacctg aagagcgtc ctctgccttg 540
gacaccatcc cctcctagca caaggagtgc ccgccttgag tgacatgcgg ctgcccacgc 600
tcctgccctc gtctccctgg ccacccttgg cctgtccacc tgtgctgctg caccaacctc 660
actgccctcc ctcgccccca cccaccctct ggtccttctg accccactta tgctgctgtg 720
aatttttttt ttaaatgatt ccaaataaaa cttgagccca ctyctaaaaa aaaaaaaaaa 780
aaaaaaaaag gggccc 796
```

<210> 172

<211> 478

<212> DNA

<213> Homo sapiens

<400> 172

```

aattcggcag agcctggttg cagggcagct aggggtctct gcattctcca catggtctca 60
tgcccccttt tgtcccctac aggaggactt gaggccatct gcccccaac aggaggggtga 120
ggcatccaaa gagaaagagg aagtggcaga ggaggccag agtgggggag actagagggc 180
tacaggccag cgtggatgac ctgaagagcg ctctctgccc ttggacacca tcccctccta 240
gcacaaggag tgccgcctt gagtgacatg cggctgcccc cgctcctgcc ctggtctccc 300
tggccaccct tggcctgtcc acctgtgctg ctgcaccaac ctactgccc tcccctcgcc 360
ccaccacccc tctggtcctt ctgacccac ttatgctgct gtgaattttt tttttaaatg 420
attccaaata aaacttgagc ccactcctaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 478

```

<210> 173

<211> 656

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (59)

<223> n equals a,t,g, or c

<400> 173

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tttcccaatg cctgccacca cggagactca gggccacctg ccaccctccc tcgtgcent 60
ctgcccttgg gatggggcgc tcctgaatgt acgtgggccc cgggtgtttac aaggaggtga 120
tcactacaaa cctctgccag aagcaggtgg tggagaagat accactgccc ttttttgcca 180
tgtccctgag cctgtccccc gggaccaccc tcctggctgt tggttttgcg gagtgcacgc 240
tgaggctggt agactgtgcc atggggactg cccaagactt tgccggccac gacaacgcag 300
tgcacctgtg caggtttaca cktccgccca ggctgctctt cacggccgcc cgcaacgaga 360
tccttggtgt ggaggtcccc ggctctgag atgcagcagg gactgtggtg gtgggcatca 420
acgcctggtc atgccaggca cctggacaca ggcttgccag aggcgccagg ttgtcaatgg 480
cctcatgctg ggacaggcca ggattcacgt aaatcgctg gagcaagctg ttgtaaattt 540
ggcgccctgt gaatactttc atacctgtt cccttttgcc taagaaatct ttaatgtttc 600
tatcttgtaa taaacatggg catttattgc aaaaaaaaaa aaaaaaaaaa aaaaaa 656

```

<210> 174

<211> 1891

<212> DNA

<213> Homo sapiens

<400> 174

```

gagccccctc cgagagggga gaccagcggg ccatgacaag ctccaggctt tggttttcgc 60
tgetgctggc ggcagcgttc gcaggacggg cgacggccct ctggccctgg cctcagaact 120
tccaaacctc cgaccagcgc tacgtccttt acccgaacaa ctttcaattc cagtacgatg 180
tcagctcggc cgcgcascgg gctgtcagc cctcgacgag gccttcacgc gctatcgtga 240
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ggagaagaat gtgttggttg tctctgtagt cacacctgga tgtaaccagc ttctactttt 360
ggagtacgtg gagaattata ccctgacctt aaatgatgac cagtgtttac tcctctctga 420
gactgtctgg ggagctctcc gaggtctgga gacttttagc cagcttggtt ggaaatctgc 480
tgagggcaca ttctttatca acaagactga gattgaggac tttccccgct ttctcaccg 540
gggcttgctg ttggatacat ctgcaccata cctgccactc tctagcatcc tggacactct 600
ggatgtcatg gcgtacaata aattgaacgt gttccactgg catctggtag atgatccttc 660
cttcccatat gagagcttca cttttccaga gctcatgaga aaggggtcct acaaccctgt 720

```

```

caccacacatc tacacagcac aggatgtgaa ggaggtcatt gaatacgcac ggctccgggg 780
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ccctgggatt actgactcct tgctactctg ggtctgagcc ctctggcacc tttggaccag 900
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa g 1891

```

<210> 175

<211> 2161

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2153)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2160)

<223> n equals a,t,g, or c

<400> 175

```

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tgctccgcgc ggctgctgca gcaggaagaa gagattaaat ctctgactgc tgaatttgac 120
cggttgaaaa actgtggctg ttaggagct tctccaaatt tggagcagtt acaagaagaa 180
aattttaaaat taaagtatcg actgaatatt cttcgaaaga gtcttcaggc agaaaggaac 240
aaaccaacta aaaatatgat taacattatt agccgcctac aagaggctctt tggatcatgca 300
attaaggctg catatccaga tttggaaaat cctcctctgc tagtgacacc aagtcagcag 360
gccaaagtgt gggactatca rtgtaatagt gctatgggta tttctcagat gctcaaaacc 420
aaggaacaga aagttaatcc aagagaaatt gctgaaaaca ttaccaaaaca cctcccagac 480
aatgaatgta ttgaaaaagt tgaaattgct ggtcctgggt ttattaatgt ccacttaaga 540
aaggattttg tatcagaaca attgaccagt cttctagtga atggagttca actacctgct 600
ctgggagaga ataaaaaggt tatagttgac ttttcctccc ctaatatagc taaagagatg 660
catgtaggcc acctgaggtc aactatcata ggagagagta taagccgcct ctttgaattt 720
gcagggtatg acgtgctcag gttaaatcat gtaggagact gggggacmca gtttggcatg 780
ctcatcgctc acctgcaaga caaatattcca gattatctaa cagtttcacc tcctattggg 840

```

```

gatcttcagg tcttttataa ggaatctaag aagaggtttg atactgagga ggaatttaag 900
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tggaagctta tctgtgatgt ctcccgccaa gagttaaata aaatctatga tgcattggac 1020
gtctctttta tagagagagg ggaatccttc tatcaagata ggatgaatga tattgtaaag 1080
gaatttgaag atagaggatt tgtgcagggt gatgatggca gaaagattgt atttgtccca 1140
gggtgttcca taccattaac catagtaaaa tcagatggag gttataccta tgatacatct 1200
gacctggctg ctattaaaca aagactatct gagggaaaag cagatatgat tatctatgtt 1260
gtggacaatg gacaatctgt gcacttccag acaatatttg ctgctgctca aatgattggg 1320
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gccaatattg atgaagaaat gctccaaaaa gctgctcgag aaaccaagat tcttttggt 1740
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gggtttgata tcctgggaat aaaacctgtc caaaggatgt aatccttcat aggtttgaac 2040
actgtgtgtt ttaccaaaag tgccattggc actgtttgct tttttacaat catgtggaca 2100
caagcataag taaagaaaat ttgtcaacca gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2160
a

```

<210> 176

<211> 2411

<212> DNA

<213> Homo sapiens

<400> 176

```

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gccagagaaa aaggtagaat ggacaagtga cactgtggac aatgaacaca tgggcccgcg 180
ctcatcmaaa tgctgctgta tttatgagaa acctcgggcc tttggcgaga gctccacgga 240
aagtgatgag gaggaagaag agggctgtgg tcatacacac tgtgtacgtg gccaccgcaa 300
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ttcccagccc cctccagggc caatgcagca ctaaatccct ctctcctcca gcattcctgt 420
gtctgtctgg ccctaaatgt atccatgtgg ctacttctcc agccccctcc ttccctctct 480
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gaacacttaa attgggtttt caacagtccc agctttcact gccagggtcc cagtcagatt 780
ccagggaattt gcgcctaac tttgcttgc aatcctggt tagagctat ccactaaaat 840
atttaaatcct aattcttagt ccttgctgt gagatatgag gtcttacagg agacctcaga 900
gtccccagcc cttctcctcc tgctaaccct tctcacacc tcaagaggag ttagaaaaga 960
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agccgactgt ctccctctgc tttgttttt cagcttcaga gacagatcca atatagtccc 1140
agggacctg gtctctggga gaggaaggaa gagggaggga gcaaagagat tggggtatgt 1200
cccctgtagt acactcttac ctcttacttc ctgactttg atttctccgg cagcccagat 1260

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```

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ttgccacaga tgcacaaaat aaataaccca aaatcacaaa atgtgttaaa tatgggcccc 1440
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gtattcccag gttkaggarg agagagggga aatagcacca ttggttcctt tccgtgagta 1560
tgtgcgggga gaagtttcaa gaaggttctt atggaaaaaa ggctgtgagc atagaaagca 1620
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acaaagcttc ccagaggcca cagggccaga ccagagtcaa gcctcttgtt ttaggagaaa 1740
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ggcctggaag gtaaagcagg tcgagtgagc ggccgctcgt gagagccacc ggccccgctc 2340
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tcgggtgccg t 2411

```

<210> 177

<211> 1338

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1234)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1276)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1289)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1326)

<223> n equals a,t,g, or c

<400> 177

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attactaaca tctttttttt ttatgagaaa tacttttccc ataaccaaaa aattcagtga 120
gcagaatggc cttgcttgag gtttttgcaa atctctcggg tgtctggctt agtgggaggc 180
agctgggccc tcatacctgc ctccgcactt cagctgtttg acataaaccc agcttcgtgt 240

```

```

gagtgaagg gaagggcctg gggaccctca gaggttctcg gaccacactt tgagaactcc 300
tcgtctggaa gacaggcctg gggatgccat gtggggtgag ggcttacggg cttggtgtcg 360
ctttgtggag aaccgctggt gtctgaagcg ggtgtcagcc ccaactgcacc ttggtcttct 420
gggctgtcct gatgccgagg ccacttccc agccatgctg actttgcctc tttcccctcc 480
cagcagaaaa atggctacaa acttcctagc acatgagaag atctgggtcg acaagttaa 540
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ccagaaatcc ctggctggaa gctcaggccc cggggcctcc agcggcacca gcggagacca 720
cggtagctc gtcgtccgga ttgccagtct ggaagtggag aaccagagtc tgcgtggcgt 780
ggtacaggag ctgcagcagg ccatctccaa gctggaggcc cggctgaacg tgctggagaa 840
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agtggagccc ccagccaaga agccagccac accagcagag gatgacgagg atgatgacat 960
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catcctgtcg gatttcaagc cttggggatg atgagacgga catggctcag ctggaggcct 1140
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tacggttatc cgaagctaa caatttcagt tgnngttgga ggacgacaag tgggggacaa 1260
cttgcctggg gagganttca ccatttttna ggagcactgc aattttcaa tcgcattttt 1320
caacanattt gaagcccc 1338

```

<210> 178

<211> 1614

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1213)

<223> n equals a,t,g, or c

<400> 178

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cctctaaagc tgagagcttg attccagggc ctgccctgct cctggtggca ccagtgggc 120
tgtactactg gtacctgggc accgagggcc agatcttcat cctcttcatc ttacaccttc 180
tcgccatgct ggcctcgcgc ctgcaccaga agcgaagcc cctctccttg acagcaacgg 240
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gctgtggaat gaccctgttc tcaggaagaa gtaccggggt gtcacttacg tccctragcc 360
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gaggatgga gacaccctgg cccccaggag ctggaggcac cggccactcc cctggcattc 1140
cagctttgca ggtgacctc ctctacccaa agctctgtcc ccctgctccc actccagaag 1200

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```

aactgcggca cgngcttcgg gcagcctagc cacaggcttt gagcgctgc attcctgggg 1260
gctggagggt ggggtgccaa aggccttgag caaaagccag agctcctctc atcaaagcct 1320
ttacaagggtg ctgggcccag aggcctttgcc ttgacagagt ggcccagggt ttcaagggtg 1380
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gggaagggtgac ccacaggaag tcacagtgggt gccagggat gtgtcagccc ccagccacgg 1500
ggacgcggga ttcaagaatg aagtaaatac agtcacagcc ccaaaaaaaaa aaaaaaaaaa 1560
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa      1614

```

<210> 179

<211> 4292

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (654)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (4288)

<223> n equals a,t,g, or c

<400> 179

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ggacattctg cagatgttca tgcccttttg aaatgttatc tctgctaaag tcttcattga 120
caaacagacc aatctgagca agtgcttttg ttttgtttag tacgacaatc cagtctctgc 180
acaagctgct atccaagcta tgaatggctt tcagatcggc atgaaacgct tgaagggtga 240
gctgaagcgt tccaaaaacg acagcaaacc ttactgatcc taaccocaga ggctccctgc 300
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acctcacatc atatttggtt ctccactga cctttgatct agtttgacct ttgaaatttg 480
catgtgacct catctagcta tgaattctgg gaagtcaatg tgaaaaacat tgctgcattc 540
atgcaagact gaaatttatt attagacaaa ttcattatag aaaaaacctg tggcaaaaac 600
gtttctttct tatttttttt cttttcctaa aacagacttg aaagtattat acangggatt 660
ggcattcttc ccggtcactg gtaacaatag caatatgtgt ccagggacac agaattgttg 720
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atctctctct gatgtttttt gtaagacatt gtataagtc ccatgtccca cttttttaac 1620

```

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cactccgcac atcagtgtctg tgaaggcaac ctccaccatgt attttcttca taatctatgg 1680
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tggtgatgac tttttatact gtcatgattt gagtttgttt tggggtgttt ccaatttgga 1800
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agatccaaaa gaaaacagaa aacaattcca cgaggccaat ctaaaggga aaaatcctac 1920
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aacagtcaaa cttatttttg taatgtatgt tattgtgtga tgcagttttt tgcttctgtc 4200
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa
4292

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<210> 180

<211> 243

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (235)

<223> n equals a,t,g, or c

<400> 180

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cagctcctcr cgccatcacc atcgccgccc cgggttccac ctrccccaac agcccctgct 120
ccagagggaa gtgtggtgtg tgggcacaac gggaaacgct aaccaggcac agagctcaac 180
ggagcagaca ctgctgaagc ccaagtgaga aaccacggcg ctttggcgtg taacntggaa 240
tat 243
```

<210> 181

<211> 813

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (266)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (723)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (726)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (738)

<223> n equals a,t,g, or c

<400> 181

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aattcggcag agaccaggtg tacctgagct acaataacgt ctccctccttg aagatgcttg 60
tggccaagga caactgggtg ctgtcctcgg agatcagtcg ggtccgcctg tacactctgg 120
aggatgacaa gttcctctcc ttccacatgg agatgggtgg gcattgtggat gcagmccagg 180
ccttcctgct gctctcggac ctgmgtcaga ggccagagtg ggacaagcac taccggagcg 240
tggagctagt gcagcaggta gacranggac gacgccatct accacgtcac cagmcctgmc 300
ctcggagggtc acacaaagcc ccaggacttc gtgatcctgg cctcgaggcg gaagccttgt 360
gacaatgggg acccctatgt catcgcgctg aggtcgggtc cgctgcccac acaccgagag 420
acgccagagt acagacgcgg agagaccctc tgctcaggct tctgcctctg gcgcgagggg 480
gaccagctga ccaaggtagc ctgtagtaga ctcgggtcct gtccacagcc ctagctgcca 540
gcaatgctgt cctcacagag gcatagtcgc cccagctgg gtgtgtgctc actgtgacgg 600
tggcccgggg ggaggtatgcc agcagcctgc ctatggytgc cagctgtgct gtgagcccag 660
cagcatggcc tgcattctggg aagggaacac ggttggtccag agcccctggc acaactgctg 720
agncanatgc tgtggagnca gctgttacct tgtaagccac tggcccagca cctgcctaca 780
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137

gggccagcct ggtggccaca gtgcacgtgg ggg

813

<210> 182

<211> 822

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (37)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (49)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (370)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (567)

<223> n equals a,t,g, or c

<400> 182

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ggttttacat gaccgcagtc gccctcagtt tcaccncta ggaatcggn c tggggatgca 60
ccgtgctact ctcttcctcc aggcgggtcc ccggcgctg cgcgcgatcc atgtccatgt 120
ccgcgcctat caataaagtt gctcacttgt tgccggcccc ctagmccgaa aggttgccg 180
cgcagmccga gaagtctcgc gatagccagc cgcggtgcc cttgcgttc ccgagctggc 240
ggggtccgtg gtgcgggac gagattgcgg gctatggcg cgaagtttt cgtcagtact 300
gggatatccc cgtggcacc gattgccacc gcaaagccta cagcaccacc agtattgcca 360
gcgtcgctgn cctgaccgcc gctgcctaca gagtcacact caatcctccg ggcaccttcc 420
ttgaaggagt ggctaagggt ggacaataca cgttactgc agctgctgtc ggggccgtgt 480
ttggcctcac cacctgcac agcgcctatg tccgcgagaa gcccgcacac cccctgaact 540
acttcctcgg tggctgcgcc ggaggcntga ctctgggagc acgcacgcac aactacggga 600
ttggcgccgc cgctgcgtg tactttggca tagcgccctc cctggtcaag atgggccggc 660
tggagggctg ggaggtgttt gaaaaaccca aggtgtgagc cctgtgcctg ccgggacctc 720
cagcctgcag aatgcgtcca gaaataaatt ctgtgtctgt gtgtgaaaaa aaaaaaaaaa 780
aaaaaaaaat yggggggggg cccskaacca attkccctta ag 822

```

<210> 183

<211> 1095

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1082)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1094)

<223> n equals a,t,g, or c

<400> 183

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gcgcggaggc ggcgggcgag cctcctcctg ctgctgctgc gccccatccc cccgcgggcc 60
gccagttcca gcccgcaccc cgcgtcgggt cccgcgcccc tccccgggcc ccgccatggg 120
cctcaccgtg tccgcgctct ttctcgggat cttcgggaag aagcagatgc ggattctcat 180
ggttggtctg gatgcggtg gcaagaaccac aatcctgtac aaactgaagt tgggggagat 240
tgtcaccacc atcccaacca taggcttcaa tgtagaaaca gtggaatata agaacatctg 300
tttcacagtc tgggacgtgg gaggccagga caagattcgg cctctgtggc ggcactactt 360
ccagaacact cagggcctca tctttgtggt ggacagtaat gaccgggagc gggccaaga 420
atctgctgat gaactccaga agatgctgca ggaggacgag ctgcgggatg cagtgtgct 480
ggtatttgcc aacaagcagg acatgcccac cgccatgccc gtgagcgagc tgactgacaa 540
gctggggcta cagcacttac gcagccgcac gtggtatgtc caggccacct gtgccacca 600
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tcccggactc ctacggcagt gccctttcct cccacttttc ctccccata gccacaggcc 780
tctgtcctg ctctgcctg catgttctct ctgttggtgg agcctggagc cttgtctct 840
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tgtactctag gggccagggt gggaggggga aggtgagggc ttcgggtggt gctataatgt 1020
ggcactggat cttgagtaat aaatttgctg tggtttgtaa aaaaaaaaa aaaaaacccc 1080
gnggggggcc ccgna 1095
```

<210> 184

<211> 3675

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2204)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3329)

<223> n equals a,t,g, or c

<400> 184

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gcgagaaccg cctggagagc ctgccccgc agatgcgccg cctggtgcac ctgcagacgc 60
tcgtgtctaa tggaaacccc ctgctgcatg cacagctccg gcagctccca gcgatgacgg 120
ccctgcagac cctgcacctg cggagaccca gcgcacccag agcaacctgc ccaccagcct 180
ggagggtctg agcaacctcg cagacgtgga tctgtcctgc aatgacctga cacgggtgcc 240
cgagtgtctg tacacctctc ccagcctgcg ccgcctcaac ctcagcagca accagatcac 300
ggagctgtcc ctgtgcatag accagtgggt gcacgtggaa actctgaacc tgtcccga 360
tcagctcacc tcaactgccct cagccatttg caagctgagc aagctgaaga agctgtacct 420
```

gaattccaac aagctggact ttgacgggct gccctcagggc attggcaagc tcaccaacct 480
 ggaagagttc atggctgcc aacaacacct ggagctgggc cctgaaagtc tctgcaggtg 540
 cccaagctg aggaacttg tcctgaacaa gaaccacctg gtgacctcc cagaagccat 600
 ccatttctctg acggagatcg aggtcctgga tgtgcgggag aacccaacc tggatcatgcc 660
 gccaagccc gcagaccgtg ccgctgagtg gtacaacatc gacttctcgc tgcagaacca 720
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cacgtgtgaa gccccctcac tcttccgcta gggataaagc agatgtggat gccctttaag 3600
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gatctagaac tagtc 3675
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<210> 185

<211> 1040

<212> DNA

<213> Homo sapiens

<400> 185

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cccagccac aatgaccag acctctagct ctcagggagg ccttggcggt ctaagtctga 180
ccacagagcc agtttcttcc aaccaggat acatcccttc ctcagaggct aacaggccaa 240
gccatctrct cagcactggg accccaggcg caggtgtccc cagcagtgga agagacggag 300
gcacaagcag agacacattt caaactgttc ccccaattc aaccaccatg agcctgagca 360
tgaggggaaga tgcgaccatc ctgcccagcc ccacgtcaga gactgtgctc actgtggctg 420
catttggtgt tatcagcttc attgtcatcc tgggtggtgt ggtgatcacc ctagttgggtg 480
tggtcagcct gaggttcaag tgcggaaga gcaaggagtc tgaagatccc cagaaacctg 540
ggagttcagg gctgtctgaa agctgctcca cagccaatgg agagaaagac agcatcacc 600
ttatctccat gaagaacatc aacatgaata atggcaaca aagtctctca gcagagaagg 660
ttctttaaaa gcaactttgg gtcccatga gtccaaggat gatgcagctg ccctgtgact 720
acaaggagga agagatggaa ttagtagagg caatgaacca catgtaaatt attttattgt 780
ttcatgtctg cttctagatc taaaggacac tagcattgcc ccagatctgg gagcaagcta 840
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cacctctca gagccacagg aaagaggagg tgacagagag agagcaagga aagtgatgag 960
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aaaaaaaaa aaaaactcga 1040
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<210> 186

<211> 817

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (26)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (76)

<223> n equals a,t,g, or c

<400> 186

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ancagctata gatcatgaca ggcaanggta nactgacagt acggtcggat tcccgggtcs 60
acccacgcgt ccgcangagc ggccgggtgg cgggaggaac cgttacggga actgaagttg 120
cggattaagc ctgatcaaga tgacaacctc ccaaaagcac cgagacttcg tggcagagcc 180
catgggggag aagccagtgg ggagcctggc tgggattggg gaagtcctgg gcaagaagct 240
ggaggaaagg ggttttgaca aggcctatgt tgtccttggc cagtttctgg tgctaaagaa 300
agatgaagac ctcttcggg aatggctgaa agacacttgt ggcgccaacg ccaagcagtc 360
ccgggactgc ttcggatgcc ttcgagagtg gtgcgacgcc ttcttgatgat gctctctggg 420
aagctctcaa tccccagccc tcatccagag tttgcagccg agtagggact cctcccctgt 480
cctctacgaa ggaaaagatt gctattgtcg tactcacctc cgacgtactc cggggtcttt 540
tgggagtttt ctcccctaac catttcaact ttttttggga ttctcgctct tgcatgcctc 600
ccccgtcctt tttcccttgc cagttccctg gtgacagtta ccagctttcc tgaatggatt 660
cccgccccca tccctcacc cccacctcac ttccaatccg ttgatacca ttggtcct 720
tttttggcag aacagtcact gtccttgtaa agtttttttag atcaataaag tcagtggctt 780
tcaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 817
```

<210> 187

<211> 1080

<212> DNA

<213> Homo sapiens

<400> 187

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gctgcacgcc gcggtacttg gggccagggtg cctggtggag ctgctcgtgg cgcacggggc 120
cgacctgaac gcaaagtccc tgatggacga gacgccccct gatgtgtgcg gggacgagga 180
ggtgcggggc aagctgctgg agctgaagca caagcacgac gccctcctgc gcgcccagag 240
ccgccagcgc tccttgctgc gccgccgcac ctccagcgcc ggcagccgcr ggaagggtgg 300
gaggcggttg agcctaacc agcgcaccga cctgtaccgc aagcagcacg cccaggaggc 360
catcgtgtgg caacagccgc cggccaccag cccggagccg cccgaggaca acgatgaccg 420
ccagacaggc gcagagctca ggccgcgcgc cccggargag gacaaccccg aagtggtcag 480
gccgcacaat ggccgagtag ggggtcctcc agtgcggcat ctatactcca agcgactaga 540
ccggagtgtc tcctaccagc tgagccccct ggacagcacc acccccaca ccctgggtcca 600
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gcgaccccca cctgagggggc ccgagagccc tgagacagct gagcctggcc tgcctggtga 720
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<210> 188

<211> 1286

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature
 <222> (1245)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1254)
 <223> n equals a,t,g, or c

<400> 188
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 gcaccatgac tctagtgtc ttggtgtata ttcttacata ccttttagtg aaaatcctta 180
 tttttcatca tggcctccaa gtggtaccag ttctaagatg tctcttgatt tacctgagaa 240
 gcaagatgga actgtttttc ctctctctct gktgccaaaca tcctctacat ccctcttctc 300
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 gaaccaggag tcagctgtac tagcaactgc tccaaggata gatgatgaaa tccccctcc 420
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 atctatagaa acatattcta ctacttatcc tgacaccatg gaaaattcaa catcttcaa 780
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 aaacatgaaa aagartatct gtaattcttg cccaccaaac aagcctgcag aatctgttca 900
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 aggrccaagg aatccaccac caacttgga tatttaataa aactccagat ttataataat 1020
 atgggtgca agtacacctg caaataaaac tactagaata ctgctagtta aaataagtgc 1080
 tctatatgca taatatcaaa tatgaagata tgctaagtgt ttaatagctt ttaaaagaaa 1140
 agcaaaatgc caataagtgc cagttttgca ttttcatatc atttgcatg agttgaaaac 1200
 tgcaataaaa agtttgtcac ttgagcttat gtacagaatg ctatntgggg aacnctttta 1260
 ggatggggtt tatttttcca tttttg 1286

<210> 189
 <211> 1738
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (1480)
 <223> n equals a,t,g, or c

<400> 189
 gcggcgccct cggagccaaa ggcgcgcggc ggacacggcg gggccctcgc gcgcctggag 60
 acgatgccaa agctgcaggg cttcgagttc tggagccgca ccctgcgagg ggcccggcac 120
 gtcgtggccc ccatggtgga ccagagcgag ctggcctgga ggctgctgag ccggcgccac 180
 ggggcacagc tctgtacac gcccatgctg catgcccagg tctttgtccg cracgccaac 240
 taccggaagg agaacctgta ctgcgaggtg tgcccaggg accggcccct catcgtgcag 300
 ttctgtgcca atgaccgga ggtgtttgtt caggcggtc tcctggctca ggattactgt 360
 gacgccattg acctgaactt gggctgcccc cagatgatag ccaagagagg tcactatggc 420

```

gcctttctgc aggacgagtg ggacctgctc caaagaatga ttttgctggc ccacgagaaa 480
ctctctgttc ctgtcacgtg caaaatccgt gtcttcccgg agattgacaa gaccgtgagt 540
acgcccagat gctggagaag gccggctgcc agttgctgac ggtgcacgga cgcaccaagg 600
agcagaaggg gcccctgtcg ggtgcagcgt cctgggagca tatcaaggct gtgcggaagg 660
ctgtggccat ccctgtgttt gctaacggga acatccagt cctgcaggac gtggagcgct 720
gcctccggga cacgggtgtg cagggcgtca tgagcgcaga gggcaacctg cacaaccccg 780
ccctgttcga gggccggagc cctgccgtgt gggagctggc cgaggagtat ctggacatcg 840
tgccggagca cccctgcccc ctgtcctacg tccgggcccc cctcttcaag ctgtggcacc 900
acacgctgca ggtgcaccag gagctgcgag aggagctggc caaggtgaag accctggagg 960
gcatcgctgc tgtgagccag gagctgaagc tgccgtgtca ggaggagata tccaggcagg 1020
agggagcgaa gccaccggc gacttgccct tccactggat ctgccagccc tacatccggc 1080
cggggcccag ggaggggagc aaggagaagg cagggtgcgcg cascaagcgg gccctggagg 1140
aagaggaggg tggcacggag gtcctgtcca agaacaagca aaagaagcag ctgaggaacc 1200
cccacaagac cttcgacccc tctctgaagc caaaatatgc aaagtgtgac cagtgtggaa 1260
acccaaaggg caacagatgt gtgttcagcc tgtgccgcgg ctgctgcaag aagcgagcct 1320
ccaaagagac tgcagactgc ccaggtcacg gattgctttt taaaaccaa ttggagaagt 1380
ctctggcctg gaaagaggcc cagcctgagc tgcaggagcc tcagccagca gcacctggaa 1440
caccaggtgg cttctccgaa gtcatgggca gtgccctggn ctgaaggccc acaaccccca 1500
ccccaggac tgctgtctga gcctggacac gtccacttta agaaaatgcc ttttactcag 1560
ggaatctcct gctacttaat gtgaaagac acgcccattg ccccttcgc cactctggg 1620
ggcctggaaa tgctgcagtg gggagcaggc ccaggctgg acctgccctg tcctcagcac 1680
gcgtgtgcaa aagtgaacaa taaatcattt caaagatgaa aaaamaaaa aaaaaaaa 1738

```

<210> 190

<211> 1923

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1829)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1875)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1910)

<223> n equals a,t,g, or c

<400> 190

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agcacatcaa atgccccac tccaagtacg ggtgcacgtt catcgggaa caggacactt 60
acgagaccca cctggagact tgccgcttcg agggcctgaa ggagtttctg cagcagacgg 120
atgaccgctt ccacgagatg cacgtggctc tggcccagaa ggaccaggag atcgccttcc 180
tgcgctccat gctgggaaag ctctcggaga agatcgacca gctagagaag agcctggagc 240
tcaagtgtga cgtcctggac gaaaaccaga gcaagctcag cgaggacctc atggagttcc 300
ggcgggacgc atccatgtta aatgacgagc tgtccacat caacgcgcgg ctgaacatgg 360
gcatcctagg ctccacgac cctcagcaga tcttcaagtg caaagggacc tttgtgggcc 420

```

```

accagggccc tgtgtggtgt ctctgcgctt actccatggg tgacctgctc ttcagtggct 480
cctctgacaa gaccatcaag gtgtgggaca catgtaccac ctacaagtgt cagaagacac 540
tggagggcca tgatggcatc gtgctggctc tctgcatcca ggggtgcaaa ctctacagcg 600
gctctgcaga ctgcaccatc attgtgtggg acatccagaa cctgcagaag gtgaacacca 660
tccggggcca tgacaacccg gtgtgcacgc tgggtctctc acacaacgtg ctcttcagcg 720
gctccctgaa ggccatcaag gtctgggaca tcgtgggcac tgagctgaag ttgaagaagg 780
agctcacagg cctcaaccac tgggtgcggg ccctggtggc tgcccagagc tacctgtaca 840
gcggctccta ccagacaatc aagatctggg acatccgaac ccttgactgc atccacgtcc 900
tgcagacgtc tgggtggcagc gtctactcca ttgctgtgac aaatcaccac attgtctgtg 960
gcacctacga gaacctcatc cacgtgtggg acattgagtc caaggagcag gtgcggaccc 1020
tcacgggcca cgtgggcacc gtgtatgcc tggcggtcat ctgcagcca gaccagacca 1080
aagtcttcag tgcatcctac gaccgggtccc tcagggtctg gagtatggac aacatgatct 1140
gcacgcagac cctgctgcgt caccagggca gtgtcaccgc gctggctgtg tcccggggcc 1200
gactcttctc aggggtgtg gatagcactg tgaaggtttg gacttgctaa caggatccag 1260
ggcaggctgt ggtttccctc gaaccagccc tggaccttcc tgagccaggc tggccacatg 1320
gggtgtgtctc ggggtttctg cctgccccgt gggcataggc ggacaggctc tggcagcccg 1380
gcagtgcctc ccccgctcca tgctcggcga gcctccctct actcggcact gtccttgtg 1440
cccagccctc ctctgggtgc caggtaacgc gcttgccccg gcccaccctc catccccacc 1500
ctccatcccc accctagatg gagcgagggc ctttttactc accttttcta ccgtttttag 1560
actgtatgta gattttggtta cctcctggtt gaaataaatg ctccacagac tgtggctgtg 1620
agtggggaca gctcctcggg acaagggggc tgtgtgtggc cttgagggtg gtgtgcacag 1680
gcactggctg ctgtgagtg gggggcatgg ggcagtttcc tttggtggac cccaggaytt 1740
cggsgcamtc cggggsctcc cctccctgct aggaggcaca ccctcagagg agctgcaagc 1800
ccgtggctgc ctgctacatg ccctgcttnc acgtggctgc acgctgacac acccacattc 1860
accaaacca cccnggccct gggacgcaac cacgccagga ggaggacacn ggccgccgag 1920
agc 1923

```

<210> 191

<211> 250

<212> DNA

<213> Homo sapiens

<400> 191

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ccaagtgtgt tgatacatta agctatgaga catctaaaat aatgaaactt ggaacttagt 60
ggaacatgta catgttttca gcatacttaa acccaaaaat cattaatttt cagaacttaa 120
tcagtgtctt tacatttgtt ttttctttta tgctagtgg aaatggagga tgaaratata 180
attgrtgtgt tccaacagca gacgggrggt gtctactgaa aagggaacct gcttctttac 240
tccagaactc 250

```

<210> 192

<211> 1902

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (8)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (763)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1898)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1900)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1901)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1902)
<223> n equals a,t,g, or c

<400> 192
ngggacgntg gtagaccanc gcgtaccgct gagtcaratt ttggcatcaa cttgaagggc 60
ccaaaaatca aaggaggtgc ggatgtttca gggggtgtca gtgcccara catcagcctt 120
ggtgaagggc attttagtgt taaaggttcc gggggtgagt ggaagggacc ccaagtctcc 180
tctgctctca acttggaacac atctaagttt gctgggggcc ttcatttctc aggaaccaag 240
gtggaaggag gtgtgaaagg aggtcagatt ggactccagg ctcttgggct gagtgtgtct 300
gggcctcaag gtcacttga aagtggatct ggaaaagtaa cattccctaa aatgaagatc 360
ccaaaattta ccttctctgg ccgtgagctg gttggcagag aaatgggggt ggatgttcac 420
ttccctaaag cagaggccag catccaagct ggtgctggag acggcgagtg ggaagagtct 480
gaagtcaaac tgaaaaagtc caagatcaaa atgcccagtg ttaatttttc caaacctaaa 540
gggaaaggtg gtgtcactgg ctcaccagaa gcatcaattt ctgggtccaa aggtgacctg 600
aaaagttcaa aggccagcct gggctctctg gaaggagagg cagaggccga agcctcttca 660
ccgaaaggca aattctcctt atttaaaagt aagaagccac ggcaccgctg caaatcatt 720
cagtgatgaa agagagttct ctggaccttc caccgccagc ggnacgctgg agtttgaagg 780
tggggaagtg tctctggaag gtgggaaagt taaagggaaa cacgggaagc tgaaattcgg 840
taccttttgt ggattgggtg caaagagcaa aggtcattat gaggtgactg ggagcgatga 900
tgagacaggc aagttacagg ggagtggggt gtccttgcc tctaagaagt cccgactgtc 960
ctcctcttct agcaatgaca gtgggaataa ggttggcatc cagcttcccg aggtggagct 1020

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gtcagtttcc acaaagaaag agtagcaggc ctttgtatgt gtgtacatat atatatatat 1080
aacaaaaacat cagccttggg tgggtgtgttc ctatataaac tccaaaggga aacacaccga 1140
ctgcctcagc aatcatgcaa agaccttgcc tggcccgggtg gcaagcgctg aaaaaccgac 1200
cgccctgtagg ctccctggaac tatacagata ggtaaagagt tccaagttcg tccagcccat 1260
gtgcaaagtc aacagtatct gccttaagat ttcatatata tatatttttt tgcattgact 1320
gctgagagct cctgtttact aagcaagctt ttgtgtttat tatcctcatt ttactgaac 1380
attgttagtt ttggggtaat ggaaaccac tttttcattg taatgacttt gggggctttt 1440
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agactggatc tgttcaaaca gcaaacgccc acagatggcc cagaggtggt ggtagtcagg 1560
gtgtgtgggt gtttttaggg ttcttttagtg ttgtttcttt caccagggg tgggtgtccc 1620
agccagtttg gtctgacgg tgagaggaaa ttagaatctg ttgcaaatt gtccaacca 1680
ccccctcaac atgaggggct tccattttct gtgttttgta agggaactgt ttccttcatg 1740
ccgccatgtt cctgatatta gttctgattt ctttttaaca aatgttatca tgattaagaa 1800
aatttccagc actttaatgg ccaattaact gagaatgtaa gaaaattgaw gctgtacaag 1860
gcaaataaag ckgttattaa cctgaaaaaa aaaaaanan nn 1902

```

<210> 193

<211> 560

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (528)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (535)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (559)

<223> n equals a,t,g, or c

<400> 193

```

ttttgcttaa agctatttan gtgacactat agaaggtagc cctgcaggta ccggtccgga 60
attcccggtt cgacccacgc gtccgggggt gcagacggag gtcaggctct cctctttcct 120
gagactggat ctgttcaaac agcaaacgcc cacagatggc ccagaggtgg tggtagtcag 180
ggtgtgtggg tgtttttagg gttcttttagt gttgtttctt tcaccaggg gtggtggtcc 240
cagccagttt ggtgctgacg gtgagaggaa attagaatct gtttgcaaat tgtccaaccc 300
acccctcaa catgaggggc ttccattttc tgtgttttgt aagggaactg tttccttcat 360
gccgccatgt tcctgatatt agttctgatt tctttttaac aaatgttatc atgattaaga 420
aaatttccag cactttaatg gccaatgaac tgagaatgta agaaaattga tgctgtacaa 480
ggcaataaaa gctgtttatt aaccttgaaa aaaaaaaaaa aaagggnggg cccgncccat 540

```

tgccctaggg ggggttaant

560

<210> 194

<211> 590

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (589)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (590)

<223> n equals a,t,g, or c

<400> 194

ctgcaggtac cgggtccggaa ttccgggtcg cccacgcgtc aggcggcggc gatgaccttc 60
 tgccggctgc tgaaccggtg tggcgaggcg gcgcggagcc tgccctggg cgccaggtgt 120
 ttccgggtgc ggggtctcgc gaccggggag aaggtcacgc aactggcca ggtttatgat 180
 gataaagact acaggagaat tcggtttgta ggtcgtcaga aagaggtgaa tgaaaacttt 240
 gccattgatt tgatagcaga gcagcccgtg agcgaggtgg agactcgggt gatagcgtgc 300
 gatggcggcg ggggagctct tggccacca aaagtgtata taaacttggg caaagaaaca 360
 aaaaccggca catgcggtta ctgtgggtc cagttcagac agcaccacca ctagagcgtg 420
 tggcacgccg ggggtcccgc agcatcctgt gagcatttcc gcggggaagc tgagcacgtg 480
 aagctcgtcg gttctgtgcg aagggtattc ctggtgctga ataaagggtg ttgctgtcaa 540
 gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaann 590

<210> 195

<211> 691

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (10)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (579)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (618)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (639)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (657)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (672)

<223> n equals a,t,g, or c

<400> 195

```
attggcatcn tctgaaagcg ttttagacag gcagaatctc tggctctccc tctctgcatt 60
ccccaccag tgaatgaatg agaactctgca tttcttgaga tcataagaat actgacatac 120
agatgagata aaactcatgt gaatatcagt ttttaaggctg gtggttcatt tgttttggtc 180
atattgagtc aggattgact aatgaactgt agaggttttg cattatgcaa atgctcttaa 240
tttcttgat taggaattag acgctcccc ccaagtctta aataatgttt taatctgtat 300
ccttttatta taagaagatt agtaatatc tacagataat aacaacaact ggtatagtat 360
attttattta cattcttcat tcttaaggaga aaatgctgag aagcttctgc agttcaagcg 420
ttggttctgg tcaatagtag agaagatgag catgacagaa cgacaagatc ttgkttactt 480
ttggacwtca agcccatcac tgccagccag tgaagaagga ttccagccta tgccctcaat 540
cacaatawga ccaccagatg accmacatct tcctactgna aaatacttgc atttcttggg 600
ctttaccttc cactctntt cctttaaaca ggattcttna aaccggaaat tgggtanctc 660
gccatttagg anccaaaaat tttgggtttt g 691
```

<210> 196

<211> 1772

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1749)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1769)

<223> n equals a,t,g, or c

<400> 196

```
gnataatgct ggccattttg cctttctgac atttccttgg gaatctgcaa gaacctcccc 60
tttcccttcc cmcaataaga ccatttaagt gtgtgytaaa caactacrga atactaaata 120
aaaagtttgg ccaaaaccaa ccatgaagct gcaaagggtgc ttgctcttac tstttcaaat 180
```

```

ttttgcaact ctartgtctc actttttaag gaacagcttg attgcaaagg agaaaataga 240
taagcaatga akttatctcc aacttcctaa aggccttatga cttctaaaaa gtgaatctat 300
cagcattcca catcagattt aaagcatcaa atgcctgtga aacagcaaaag atggttgaag 360
attgtgctca ttatgtttgt ggagtgtgta ttgattcaca gtagataacg ctggcagtaa 420
gagaaatcaa atgctaagag ttgttgaagc agaaggcggc tgattgttgg taagtcagtg 480
cagttgcata agcagtgtcg tcagaattgg tttggtgcag gcaatagatt ttgccttcaa 540
gggttcctgt ggatctcagg aaggcatcag tgttgattaa cactcataac tagggagtga 600
stggtagtta cttaagtaat tgaccaaag gaaaaggga agtaattaag gaaattggta 660
agtggaggta gtcaggargt tctygtggy cttacayag attttacagc tttggstttc 720
attttgttta gctaaagtca tggggacaac tcttcaattt agaacttaag ttgaattata 780
aaaatgatgg atataagtgg tagctgtatc tagtgaagtg tctgtcagta agtgaacat 840
tttttggtgg tggcttatcc acaaacagtt tagttgtaga ataaaactta tgagtgcacat 900
ctggaaagta accatgctaa gatggcaagc acactggaaa caattaggcc acttggcttt 960
cttttgctgt attgttttat aagcctactt tacctccag tcttggaac aagttttagt 1020
tttttattgg tttggagact agagccaata gtataatgtt ctcaaaggaa acagacttga 1080
gttgttgat tagaggaact aaccaactt atatgatttt tttttgttt ttgtcgtgta 1140
gttatggcac tgtcttattt ggaacatttg caactaggga taatacaaca tttttaactc 1200
tcatttgaca acctactact aatcacagac cacaagggtg atgaccaa attatgtggtt 1260
tttgcactcc atagttgtct tagcccaatc ttctatact cttacgatta cttgggttaa 1320
cgcytctgtg aggaccttct ggctcttgag ataccctaaa tatttaagat atttagatat 1380
cttgaagata gtataggata tagagattgt accaaatagg aatataagga gtatgttaaa 1440
atgaccagat acctgtttga tagtttactg acctagcaga tgtgtggaaa aggaatcaga 1500
tcttgattct tctgggttta tactggttgt aaaacagaat gatacagaaa atgttttcct 1560
tgtttaactg gtagttgaac atagaacttg ggtattatag atcacttttc actttttgga 1620
atgttttgta ttgaaactta ataaaacttt aacatggcaa aaaaaaaaaa aaaaaaaaaa 1680
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1740
aaaaaagana aaaaaaaaaa ggggggccnc cc 1772

```

<210> 197

<211> 675

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (657)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (671)

<223> n equals a,t,g, or c

<400> 197

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accacgcgt ccggacttcc tcttcgttaa gtcggccttc ccaacatggc gcagtctatt 60
aacatcacgg agctgaatct gccgcagcta gaaatgctca agaaccagct ggaccaggaa 120
gtggagtctt tgtccacgtc cattgtctcag ctcaaagtgg tacagaccaa gtatgtggaa 180
gccaaggact gtctgaacgt gctgaacaag agcaacgagg ggaaagaatt actcgtccca 240
ctgacgagtt ctatgtatgt ccctgggaag ctgcatgatg tggaacacgt gctcatcgat 300
gtgggaactg ggtactatgt agagaagaca gctgaggatg ccaaggactt cttcaagagg 360
aagatagatt ttctaacca gcagatggag aaaatccaac cagctcttca ggagaagcac 420

```

150

```

gccatgaaac aggccgtcat ggaaatgat agtcagaaga ttcagcagct cacagccctg 480
ggggcagctc aggctactgc taaggcctga gagtttttgc agaaatgggg cagagggaca 540
ccctttgggc gtggcttcct ggtgatggga agggctctgt gttttaatgc caataaatgt 600
gccagctggg caraaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaccccnggg 660
gggggcccgg naccc                                     675

```

```

<210> 198
<211> 557
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (451)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (461)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (464)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (488)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (492)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (495)
<223> n equals a,t,g, or c

```

```

<400> 198
tttaggtgac acgtatagaa ggtcgcctgc aggtaccggw ccggaattcc gggtcgaccc 60
acgcgtccgg gaacacaaga tgccgaaggg aagaaggcga aggggaagaa ggtggccccc 120
gcccccgccg tcgtgaagaa gcaggaggcc aagaaggctg tcaacccgct gttcgagaag 180
cggcccaaga acttcggcat cggtcaggac atccagccca agcgggacct gacgcgcttc 240
gtcaagtggc cgcgctacat ccggctgcag cggcacgcgc gatcctctac aagcggctga 300
aggtgccggc cgccatcaac cagttcacgc aggcgctgga ccgccagacg gccacgcagc 360
ttgcttgaag ctggcgcaac attaccggcc cgagacgaag caggagaaga agcagcggtt 420
gttgcccgcc gcggagaaga aarcggccgg ncaaggggga ntnccgaac aagcggsgcc 480
cgttggtntc gnaancgggg ttgaaaacgg ttcaacaagt tggttggaga acaagaaggc 540

```

gccattgggtt cggttatt

557

<210> 199

<211> 2611

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (3)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2549)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2560)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2585)

<223> n equals a,t,g, or c

<400> 199

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cgacaaggac tggaggcccc gctgtacctc acccccagg gctgggccct cttcctccag 120
cgctactacc aagtgggtcca cgaaggggca gaactcaggc acctcgacac tcagggtccag 180
cgctgtgagg acatcctgca gcagctgcag gccgtggtac cccagataga catggaaggg 240
gatcgcaaca tctggatcgt gaagccagga gccaaagtccc gcggacgagg catcatgtgc 300
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gacctcagac agtgggttcc gttaactgac tggaaaccac ttaccgtgtg gttctaccgc 480
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ccacttcccc agcctccaca ccaaggccca gctgccttct ccccatgtac tccgacacca 1380

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gggccaggtc ctcagacgac agcacagcaa gctggtgggc actaaggccc tgtcgaccac 1440
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catccataag ccacaaccac tggagaaant tttgcaactgn ttagtgtagt tggttgaatg 2580
tgggnccccg gaaagagatg ttacttggac c 2611

```

<210> 200

<211> 2316

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2280)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2282)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2302)

<223> n equals a,t,g, or c

<400> 200

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ggcacgagga aacatggagt cctgtaggca aggtcttacc tgaatcagga tgagggagtg 60
gtgggtccag gtggggctgc tggccgtgcc cctgcttgct gcgtacctgc acatcccacc 120
ccctcagctc tcccctgccc ttactcatg gaagtcttca ggcaagtttt tcaattacaa 180
gggactgcgt atcttctacc aagactctgt ggggtgtggt ggaagtccag agatagtgtg 240
gcttttacac ggttttccaa catccagcta cgactggtac aagatttggg aaggtctgac 300
cttgaggttt catcgggtga ttgcccttga tttcttaggc tttggcttca gtgacaaacc 360
gagaccacat cactattcca tatttgagca ggccagcatc gtggaagcgc ttttgcgga 420
tctggggctc cagaaccgca ggatcaacct tctttctcat gactatggag atattgttg 480

```

```

tcaggagctt ctctacaggt acaagcagaa tcgatctggt cggcttacca taaagagtct 540
ctgtctgtca aatggaggtg tctttcctga gactcaccgt ccactccttc tccaaaagct 600
actcaaaagt ggaggtgtgc tgtcacccat cctcacacga ctgatgaact tctttgtatt 660
ctctcgaggt ctaccccag tctttgggcc gtatactcgg cctctgaga gtgagctgtg 720
ggacatgtgg gcagggatcc gcaacaatga cgggaactta gtcattgaca gtctcttaca 780
gtacatcaat cagaggaaga agttcagaag gcgctgggtg ggagctcttg cctctgtaac 840
tatccccatt catTTTTatct atgggccatt ggatcctgta aatccctatc cagagttttt 900
ggagctgtac aggaaaacgc tgccgcggtc cacagtgtcg attctggatg accacattag 960
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tgactaaggt tgacataata gtccacctcc cattactttg atatctgac aaatgtatag 1260
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ctccccactg cctgtcccag agaggctttc caatgtagct cagtaattcc tgttacttta 2040
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gctgaatact ttttttttaa agccacattt cattgtctta gtcaaagcag gattattaag 2160
tgattattta aaattcgttt ttttaaatta gcaacttcaa gtataacaac tttgaaactg 2220
gaataagtgt ttattttcta ttaataaaaa tgaattgtga caaaaaaaaaa aaaagggccn 2280
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```

<210> 201

<211> 1147

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (5)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (11)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (12)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1145)
<223> n equals a,t,g, or c

<400> 201
cgcannccac nnggtggang ccgctctaga atatggatcc cccgggactg cagggagtcc 60
aaggtacagt cgcgcgctgc ggagcttggt actggttact tggcctcatg gcggtccgag 120
cttcgttcga gaacaactgt gagatcggt gctttgcca gctcaccaac acctactgtc 180
tggtagcgat cggaggctca gagaacttct acagtgtgtt cgagggcgag ctctccgata 240
ccatccccgt ggtgcacgcg tctatcgccg gctgccgcat catcgggcgc atgtgtgttg 300
ggaacaggca cggctctctg gtacccaaca ataccaccga ccaggagctg caacacattc 360
gcaacagcct cccagacaca gtgcagatta ggcgggtgga ggagcggctc tcagccttg 420
gcaatgtcac cacctgcaat gactacgtgg ccttggtcca cccagacttg gacagggaga 480
cagaagaaat tctggcagat gtgctcaagg tggaagtctt cagacagaca gtggccgacc 540
aggtgctagt aggaagctac tgtgtcttca gcaatcaggg agggctggtg catcccaaga 600
cttcaattga agaccaggat gagctgtcct ctctcttca agtccccctt gtggcgggga 660
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gctgtcctgt gccaccccat taaagtgcag ttccctccgg aaaaaaaaaa aaaaaaaggg 1140
cggcnac 1147

<210> 202
<211> 688
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (477)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (684)

<223> n equals a,t,g, or c

<400> 202

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ggagtcgggc' cgcgactgtg gtcgttttta taccttcccg cgcggacgcc ggcgctgcca 120
acggaagggc gggtaggacg gagtttcgtc atgttgacca ggcccatttg agatctttga 180
agatatactc aacgtgaggc tctgctgcca tgaagggtgaa gattaagtgc tggaaaggcg 240
tggccacttg gctctgggtg gccaacgatg agaactgtgg catctgcagg atggcattta 300
acggatgctg ccctgactgc aagggtcccc gcgacgactg cccgctggtg tggggccagt 360
gctcccactg cttccacatg cattgcatcc tcaagtggct gcacgcacag caggtgcagc 420
agcactgccc catgtgccgc caggaatgga agttcaagga gtgaggcccg acctggntct 480
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cgcccctgag ctgcaacaag gtggaaacaa gggctggagc tgcgtttgtt ttgccatcac 600
tatgttgaca cttttatcca ataatgaaa actcattaaa ctactcaaat cttaaaaaaa 660
aaawaaawaa atctcggggg gggncocg 688
```

<210> 203

<211> 304

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (269)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (287)

<223> n equals a,t,g, or c

<400> 203

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aaatgtgaaa actaaggcct tgcaagccta tggttcacc aggggtagga tcaggcacct 60
taactctaga gccattctc ctaaccactg agccatgatt gtcttacaat tttgaatact 120
gcaaaactgg aagaattgtc tggtattat ctaagctgtt cataagctgg aacaagtaga 180
tctgagggtg agaggagttc tgttttaact aggactgagt ttcaaataga gatgtttcag 240
actatagagg gggaaaaatg gcckgggang tccataaatc taagccngtt tcatggatgt 300
tttt 304
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<210> 204

<211> 417

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (380)

<223> n equals a,t,g, or c

<400> 204

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gggtcgaccc acgcgtccgc gcgggcgggg acggagctcg gcgtgcttgc tgctggaggg 60
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```

tgatggccct gcaaggctgt gggctccgac ctcaccggga gtcgamarcg agaggttcgc 120
cgaagagcga ggttctgggc gagcgtgaa cgccggcccc aagcaccg ggtctttaca 180
cagtcgcggt ccacagactc tgacgaagac gtggatctgc tctcgcttta gctgctcgcg 240
gtcctccaga tcatgtccgc gactcctgcg actccgcgcg gaaaaaaaaag tttgccaggc 300
gtggactcaa tgacytttcc aastgtgcgc ctcgytgcct ggaccgggtt gagcgcggtt 360
gcccaagttg aactttttgn ggggagggtt ttctctaagg gctgttgtct caatggg 417

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<210> 205

<211> 551

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (450)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (458)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (471)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (484)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (519)

<223> n equals a,t,g, or c

<400> 205

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tttttttttt tggtttccag agtttggtt tattttgcag tacagaaatc atctggagcc 120
gtctgagaca gacatccctg aagcggaggc tctgtcaaata caatactgcg tcgcacttrg 180
tccgttgagg aagccacacc tggggtacaa aagaagcttc tacgtttacc cgctgtacca 240
cggatttctt tcccctttgc tcttaccat tttaccagg gaaaacaccg cacagaggct 300
tccctcgga tgacgctcgg gtctggagtt gggttagaat tgtgggccc cgtgaccccc 360
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gcggggccac gcagggatgc tgttcccaan tcacgganta tctgggtggc ntcgcaatgg 480
ccantgggac agatggcacg tgaaaggggc cgttccggnt ctcaagcggc agaagcacia 540
gaccgcggag g                                     551

```

<210> 206

<211> 1101

<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (21)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (479)
<223> n equals a,t,g, or c

<400> 206
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ggccccgcg cgccccgggt cggaggcaga ccctgggtt tgggggacat gggcatttg 120
ggcgctgaa cccaagacct ctggatgagc tgccccgttc agaccatgga tcctgaggtg 180
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agccccgcc atgaccgtcg cccactgcca ggtggggacg aggccatcac tgccatctg 300
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gccaccctgg cgcctattgg ctctcgggg ccacagctgc tcctgcccct gggccttact 420
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ggtgccaccg actgggggtga cagcgaggcc tatctggcg acccactggg ggtgggcgct 540
gcactagcca cagccgatga cttccttgy ttctgccc gctccccgca ggtggctgag 600
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ggcagcccc agcaccagga cctcgctgg cagctggtg tacatgaact cttttccagt 720
gtccttcagg agatctgtga tgaggtgaac ctgcccgtgc tcaccctgag ccagcccctg 780
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cagtgcagcc tgacttctga gcaggtgagg aagcactacc tgagtggggg acccgaggcc 900
cacgagtcta caggaatctt ctttgtggag acacagaacg tgcggagatt gcccgagacg 960
gagatgtgg ctgaactctg cccctcgcca aaggcgccat catcctctac aaccgggttc 1020
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aataaacgac tttattcttg g 1101

<210> 207
<211> 515
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (428)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (439)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (449)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (456)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (474)
 <223> n equals a,t,g, or c

<400> 207
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 acactgcgag aatacaagggt ggtggggcgc tgcctgcccc ccccaaatg tcgcactccg 120
 ccgctgtatc gcatgcgaat ctttgacact aatcacgtgg tcgccaaagtc ccgcttttgg 180
 tactttgtgt ctcagctgaa aaagatgaag aagtcctcag gggaaatcgt ctactgtgga 240
 cagggtgtttg agaaatcccc cttgcgagtg aagaacttcg gcatctggct gcgctatgac 300
 tcgagaagcg gtaccacaaa catgtaccgg ggagtaccgg ggacctgacc amcgcgggcg 360
 ccgtcaccca gtggttaccg agacatgggc gcccgacacc gttgcccag cgcattcgat 420
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 agcattttcca aggattccaa gatcaattcc cattg 515

<210> 208
 <211> 269
 <212> DNA
 <213> Homo sapiens

<400> 208
 aagcattgtg ggtaaaggcc tggaggcagg aaagtgaagg acaatttcaa gaaactcagt 60
 tcatcaattt tcatcaacac cttcctgggc catgcctggg tactgagraa cccagccctg 120
 aatctggaca tcattttccc tttcagagca tagaatgcag ggggatccag ggaatgggtt 180
 aacagaagag gaagctggwt caaggagacc tttgcgtacc aggtgaagggt gtttgaactt 240
 tgttcttgca ggcaggcaga gcacggaca 269

<210> 209
 <211> 734
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (278)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (732)
 <223> n equals a,t,g, or c

<400> 209

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ccgcggacgc ccgctgagct tggcgcacgg gccgaccagg agctggtgac tgccctcatg 120
tgtgatttgc ggcggccagc ggcagggtgg atgatggact tggcctacgt ctgtgagtgg 180
gagaaatggt ccaagagcac ccaactgccc tcggtgcccc tggcctgcgc ctggtcctgc 240
cgaaatctca tcgccttcac catggacctg cgcacgantg accaggacct gacccgcatg 300
atccacatcc tggacacgga gcacccctgg gacctgcact cgatcccctc agagcaccac 360
gaggccatca cctgcctgga gtgggaccag tcaggctccc ggctcctgtc agcagatgcc 420
gacgggcaga tcaagtgtg gagcatggcg gaccacctgg ctaatagctg ggagagctca 480
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aaactggccc tgcacgtgga gaagtcgggc gcctccagct tcggggagaa gttctcccga 600
gtcaagttct caccygttct cacgctgttc ggcggcaagc catggagggc tggatcgagg 660
tgacggtcag cggcctggtc accgtgtccc tgctgwaasc agcgggcagg tgctgacgtc 720
caccgagagc tntt 734

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<210> 210

<211> 658

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (561)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (567)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (577)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (580)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (636)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (654)

<223> n equals a,t,g, or c

<400> 210

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cccgccagcg ttgaggttta tcacgacagc ctgtgccgaa aaatctggcg tgaggatgat 60
aaatggcatg tcatttttcg tgcagacggc tgggagcaac atattaccgc ccgctatctg 120
gtcggtgccg atggcgcaaa ctgatgggtg cggcgacatc tctaccggga tcatcaaadc 180
cgtaaatatg tcgctatcca gcagtgggtc gcgagaaaac atccgggtgc gttctactcc 240
tgcattcttg ataattcgat aactaactgt tattcatgga gtatcagcaa agacggktat 300
tttatctttg gcggtgccta tccaatggaa agacggtcag acgsgtttca sgacgcttra 360
agagaaaatg agcgcccttc agttccagtt tggtaagacg gtgaaaagcg aaaaatgcac 420
gggtgctgtt tccctcgcg cggcaggatt ttgtctgcgg taaggacaac gcctttcttg 480
attggtgaac ggcgggattt atcagcgcca gctcgctgga agggattagc tatgcgctgg 540
atagcacaga catttctgcg ntcgtgntac tgaacanccn gagaagctca ataccgttac 600
tggcgcgcca cccgaaactg ggttaaactc ttcggnaaga tataaaaagc catnctga 658

```

<210> 211

<211> 204

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (91)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (94)

<223> n equals a,t,g, or c

<400> 211

```

attcggagag ccatctctga cagttagagc cgatatcact ggaagatatt caatcgtctc 60
tatgcttacg acctgcagat acagtctgtt nttncacatg aagaaagtct caagttgctg 120
aagactgaat tgtaagaaaa atctccagcc cttctgtctg cagcttgaga cttgaaccag 180
agagtgtgag agctgctgtt ggag                                     204

```

<210> 212

<211> 1271

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1222)

<223> n equals a,t,g, or c

<400> 212

```

ttccgcagcc ttgccccagc ccactcccc tctcacccta ccacagagca tggtaaatac 60
caagcccagag aagacggagg aggactcaga ggaggtgagg gagcagaaac acaagacctt 120
cgtggaaaaa tacgagaaac agatcaagca ctttgccatg cttcgccgct gggatgacag 180
ccaaaagtac ctgtcagaca acgtccacct ggtgtgcgag gagacagcca attacctggg 240
catttggtgc attgacctag aggtggagga gaaatgtgca ctcatggagc aggtggccca 300
ccagacaatc gtcatgcaat ttatcctgga gctggccaag agcctaaagg tggacccccg 360
ggcctgcttc cggcagttct tcactaagat taagacagcc gatcgccagt acatggaggg 420

```

```

cttcaacgac gagctggaag ccttcaagga gcgtgtgcgg ggccgtgcca agctgcgcat 480
cgagaaggcc atgaaggagt acgaggagga ggagcgcaag aagcggctcg gcccggcg 540
cctggacccc gtcgaggtct acgagtcctt ccctgaggaa ctccagaagt gcttcgatgt 600
gaaggacgtg cagatgctgc aggacgcat cagcaagatg gacccaccg acgcaaagta 660
ccacatgcag cgctgcattg actctggcct ctgggtcccc aactctaagg ccagcgaggc 720
caaggaggga gaggaggcag gtcctgggga ccctacttg gaagctgttc ccaagacggg 780
cgatgagaag gatgtcagtg tgtgacctgc ccagctacc accgccacct gcttcaggc 840
ccctatgtgc cccttttcag aaaacagata gatgccatct cggccgctcc tgacttcctc 900
tacttgcgct gtcgagccca gcctgggggg ccgcccagc cctccctggc ctctccactg 960
tctccactct ccagcgccca ttcaagtctc tgctttgagt caaggggctt cactgcctgc 1020
agcccccat cagcattatg ccaaaggccc ggggggtccg ggaagggcag aggtcaccag 1080
gctggtctac cagtagttg gggaggggtc ccagccaagg ggcgggctct cgtcactggg 1140
ctctgttttc actgttcgtc tgctgtctgt gtcttctatt tggcaaacag caatgatctt 1200
ccaataaaag atttcagatg cnaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaacaaaaa 1260
aaaaaaaaa g 1271

```

<210> 213

<211> 1025

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (991)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1007)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1019)

<223> n equals a,t,g, or c

<400> 213

```

cggacgcgtg ggcgagcgtg atagccaaca ggaaccggga gcgggggtccc gggactggga 60
agaaaacggcg gccgggaggg ggctccgggg accatggggc tcctgacctat tctgaagaag 120
atgaagcaga aagagcgagg gctgcgactg ctcatgcttg gcctggacaa tgctggaaag 180
acaacccatcc tgaagaagtt caatggggag gacatcgaca ccatctcccc aacgctgggc 240
ttcaacatca agaccctgga gcaccgagga ttcaagctga acatctggga tgtgggtggc 300
cagaagtccc tgcggctcta ctggcggaac tactttgaga gcaccgatgg cctcatctgg 360
gtagtggaca gcgcagaccg ccagcgcatg caggactgcc agcgggagct ccagagcctg 420
ctggtggagg agcgcctggc cggagcaacc ctccctcatct ttgctaataa gcaggacctg 480
cctggagcac tgtcctctaa cgccatccgc gaggycctgg agctggactc catccgcagc 540
caccactggg gcatccaggg ctgcagcgcc gtcaccgggg agaacctgct gccgggcatac 600
gactggctcc tggatgacat ttccagccgc attttcacag ctgactgaac cactccagat 660
gccccccacc tagcagtcca ggtccctcaa ccttcaccaa acactacca tgggggggtt 720
ggagtcagcc ggccaaacta aactccccc tcctccaccc cagcctgctg ctgctactgc 780
tgcccgctgc tgctctgtgg ccaccgggt cccatggcgg gagggtgtg ccctggctgt 840

```

```

ctctctggct cctgacctgg cctttggcta ccataccaag aagagagggc tgggcgggga 900
ggagctgcta ctgtgcttac cgaggtgtg ggccatcc ttcactcagt tgtgaaataa 960
accgctcctt gccccgmaaa aaaaaaaaaa naaaaaaaaa aaaaaanccc ggggggggnc 1020
ccgga 1025

```

```

<210> 214
<211> 351
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (332)
<223> n equals a,t,g, or c

```

```

<400> 214
ggcacgagtr aactatatac ctcaaagaat tagaaaaaga agaacaaact aagctcaaag 60
ttagcagaag gaagaaata gtaaatatta cagcagaagt aaagtagagg ctagaaaaat 120
aataaaaaag atcaacaaaa tggatattgt tctcactata tgataaagac atacttgaga 180
accgcattat ttatggggaa aagaagttaa attgactcac agttccacag gctgtacagg 240
aggcatggct tagggaggcc tcagggaaac ttagratcca tgggtggaagg tgkargagga 300
agcatgcacc atcttctactg gccagagcag gnggagagag agcaaatttg g 351

```

```

<210> 215
<211> 1087
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (1075)
<223> n equals a,t,g, or c

```

```

<400> 215
gctggagtcc cagtccaccc gccacgcccg agcagggcct gtccgccttc tacctctcct 60
actttgacat gctgtaccct gaggacagca gctgggcagc caaggccctt ggggccagca 120
gtcgggagga gccacctgag gagcctgagc agtgcccgtt cattgacagc caagccccag 180
cgggcagcct ggacttggtg cccggcgggc tgaccttga ggagcactcg ctggagcagg 240
tgcagtccat ggtggtgggc gaagtgtca aggacatcga gacggcctgc aagctgtctca 300
acatcaccgc agatcccatg gactggagcc ccagcaatgt gcagaagtgg ctctgttga 360
cagagcacca ataccggctg ccccccattg gcaaggcctt ccaggagctg gcgggcaagg 420
agctgtgcgc catgtcggag gagcagttcc gccagcgtc gccctgggt ggggatgtgc 480
tgcacgccc cctggacatc tggaaagtcag cggcctggat gaaagagcgg acttcacctg 540
gggcgattca ctactgtgcc tcgaccagtg aggagagctg gaccgacagc gaggtggact 600
catcatgctc cgggcagccc atccacctgt ggcagttcct caaggagtgt ctactcaagc 660
cccacagcta tggccgcttc attaggtggc tcaacaagga gaagggcata ttcaaaattg 720
aggactcagc ccagggtggc cggtgttrgg gcatccgcaa gaaccgtccc gccatgaact 780
acgacaagct gagccgctcc atccgscagt attacaagaa gggcatcatc cggaagccag 840
acatctycca gcgsetcgtc taccagttcg tgcacccat ctgagtgcct ggcccagggc 900
ctgaaacccg ccctcagggg cctctctcct gcctgcctg cctcagccag gccctgagat 960
gggggaaaaac ggcagtcctg tctgtgtctc tgaccttcag agcccaaggt caaggagggg 1020

```

caaccaactg cccaggggga tatgggtcct cttggggcct tcgggaccct ggggncaagg 1080
ggctttc 1087

<210> 216

<211> 1977

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (8)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (11)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1873)

<223> n equals a,t,g, or c

<400> 216

cgctgcnng nacgggtccg gaattcccgg gtcgacccac gcgtccggca gaagaagagg 60
aggaggaaga tgaggaagag gaggaagaag aggaggagga ggaggaagaa gagcctcagc 120
agcgagggca gggagagaag tcagccacgc cctcacggaa gattctggac cctaactctg 180
gggagccagc tcccgtgctg tcctcccac ctctgcaga cgtctccacc ttcctggctt 240
ttccctctcc agagaagctg ctgcgcctag ggcccaagag ctccgtgctg atagccagc 300
agactgacac gtctgacccc gagaagggtg tctctgcctt cctaaagggtg tcatctgtgt 360
tcaaggacga agctactgtg aggatggcag tgcaggatgc agtagatgcc ctgatgcaga 420
aggctttcaa ctctcgtcc ttcaactcca acaccttcct caccaggctc ctctgacaca 480
tgggtctgct caagagtga gacaaggtea aggccattgc caacctgtac ggccccctga 540
tggcgctgaa ccacatggtg cagcaggact atttcccaa ggcccttgca cccctgctgc 600
tggcgcttctg gaccaagccc aacagcgccc tggaaacctg ctcttcgcc cgccacagtc 660
tgctgcagac gctgtacaag gtctagactc aaagcctctc ccatcccttg gcctggacca 720
gtgagctggg gagggactcg gatgaactga ggcgcagcct acgccattgc cttggacagg 780
actctggcca caggcagggc gggctctgtgt cccatgtgtc ctgtcagtcc cctgagtatg 840
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ggagttgccc gcgtgctgtc cttccctct gtgttgtgat tgggttgtt cctgccctgc 1140
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taccactgtg ctgaccgctc agcctgaaga gcagagaatg ccatgggtgg gactgtgggg 1260
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aaccctaaagc tggtctccag tctggggagg gagaggcagg gtccccaatg tccgagctgc 1500
atctggacgc tgctcttaaa ggacctcctg gggcagggga gcggtagggt ctggactggg 1560
cagatgctgt atgacctccc tgagcaccgc tgactgcccc atgctttccc ctttgtgtc 1620

```

tgtgtgtgtc tggctgtgcc cgggggcttc acaaataaag tcgtgtggca gcttcagaga 1680
ctcagaaact ctcactgaaa gcgggtagt ctcggggggcc gttgtacgtg gagtcccacc 1740
tcggcagagc atgcggcccc gcagcagtct gtggggcagt cagccctgca gaagggcccg 1800
gcctcggcct caggcactac ctgggaagtg gcagtcctga gtggggggccc attttcctgc 1860
ctggscacac ctnaccacgc accctgcctt tgggctgcag ctcgcttggc ttctgcgttg 1920
ctccttcact atggaagcca cctcccttgg gatcctttgc tccactgcca catatgt 1977

```

<210> 217

<211> 2815

<212> DNA

<213> Homo sapiens

<400> 217

```

aattcccggg tcgacccacg cgtccggggcg cccgcgtctg agcccagagg gctgtggagt 60
gtcccggccg gccccgagca ccccgcgct gtccgtcccc cgctccggtc ttccgctttg 120
gcttccaact agttaaatgc ccttgagcgc gggtttccgc ggcccggctc ttccgccccg 180
cggcgcgagt tgagccgttt cccgcgctg tccgcgcggg cgctccgaca gcggctctgc 240
agggtccgcg gccagcgctc ggccaccgct cggccgccac tcaaggctca cgcgtcgatg 300
tgtagctaca tagttatctg tgtacatcca cgctggggca tttttctcct gcttaatgag 360
gacttgactc gggagcaagt gtgaatcatt gccggggctg ggaaaggagg aaggcgcatt 420
taacccctc ccacccctct ccatgtccgt gtgtcactcg gctcgggtca cctggcgcg 480
ccggctcctg ggctgctgct gctgttgacg acgacgacga cgacgggggc tgctctgct 540
gtcccgggag tttcctcctg ctccggccac acagctcctg gggattgttc ctcttcgaac 600
cagaacctcg gcctgaccgg cactttggct ccaaaataac tttatttttg ggggagaaa 660
cacatcacga accagtcaaa atcgtgggtt atttctgtaa cgtgaagact tctgctctt 720
tttctttgtt tgtttttttc gtaaaccatct ggggtgtatat caaacggcaa gatgtccagt 780
aatgtcccgg cggatatgat aaatttgccg ctcatttttg taagcggaaa aacaaaagag 840
ttcctgtttt ctctaacga ttctgcttct gacattgcaa agcatgtata tgacaattgg 900
ccaatggact gggaagaaga gcaggtcagc agtccaaata ttctacgact tatttatcaa 960
ggacgatttc tacatggaaa tgtcacatta ggagcattaa aacttccttt tggcaaaaca 1020
acagtgatgc atttgggtggc cagagagaca ttaccagagc caaactctca aggtcagagg 1080
aatcgtgaga agactggaga gagtaattgt tgtgtaatcc tgtaaacact gtctgcctg 1140
tgtgatgtga tatagtcttt gtctttcatg ctgctgggac agaaaagacc cgacattgct 1200
tcagaaaccg ttcagaacag tctgcctgta aacacatgga actgaattac cacatgaaca 1260
ctgtcatctt ttctcatgaa agtaaaaaga accaagaaca tttttcactc tgatttttta 1320
tttcttgat tttttgttga gctgttttaa cacatatttg tttttgaatg cagtcaatct 1380
ccaggggaaa agttaacaag ttatctttcg tagcagaaac cattttgctg ccacaaaatt 1440
ttcatcatca gaactaataa atcaagtgtt ccaaatacaa tttgcactaa aaagattggc 1500
attattttcc tcatcagcag aatttataac agtgtgtggt atctagaaat acttatatat 1560
acaattccac actggaagac actcagcaat taatgaagt aattactggg ccaacttgag 1620
agggaaaaat ggaaaagaaa ctaaaatgtt ggggtgaattc taccaaagtc agccgtgggtg 1680
gctgcactgg cacagaatac taaactgagt gtgactatct tccactgcaac aaatgaaaaa 1740
acaaaatgtg cctgttttaa gcactcagta gagggctgat gaaactaatt ttttttcctt 1800
taagacatgc actcttgagt cctacagtaa ctgagtgtt gtttagacag cacaagaagg 1860
ggtagagtg cgtctcctag ccttaatgtg ggagggtagt ttcagtcact catcggttt 1920
cattattgtg crgaaatatt agaaaacctc attgatcaat tttatgtatt tgaatatcag 1980
caaattgaaa tttccataa ttatcattaa tttgtaacca catccagtgt catgcttact 2040
ccttagagtt cagatgaatt cttaaaatta aaaaaaact ccatagtact aattttgktt 2100
ttttatatag tttgcgtttg atattagtgc ttgcaattgt attaaagtca aaagctgatt 2160
tttatggcat acacaagaat gccacttttt cttttatttc ataccaataa tttaaagatt 2220
gatatgctaa aaacaatttg cacagcacta aagcatgagc tactttcatc taaacctgta 2280

```

```

aaaatatgaa agatttttat attttttcac tgggaagaaa ttcttcctgg atgaaattac 2340
aaatatgtgt agaatatatt taataaaaga cttataaaat acctaactac aggacttaaa 2400
atatagattg gcgcgtagta tatagaacaa tattccatat aaataagttt agcctttata 2460
aaaatgaagt tgcaggctga cattacattc tgtacttact aagtgtcaac agcccttaca 2520
aacattaaat gtaaattggt tcaaatgggtc agcgttggtt aaatgtaatc atgttatatt 2580
attcattggt aatgctttga tgaaaaggct ttatatgcag tagatctacg aaaatattgt 2640
tcatactgat cagaattaaa tttgtataga gcagagtttt aaaatgaatg taaatagcac 2700
taaacgtttt ctttctgcaa cctgtactta cagattcttc ctgtaacta aataaaaaaa 2760
aaatgatagt gcaaaaaaaa aaaaaagggt cgccgcctcg cgatctagaa ctagt      2815

```

<210> 218

<211> 1645

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (347)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1643)

<223> n equals a,t,g, or c

<400> 218

```

gcccacgcgt cgggagggcg gggacaactg ggtcttttgc ggctgcagcg ggcttgtagg 60
tgtccggctt tgctggccca gcaagcctga taagcatgaa gctcttatct ttggtggctg 120
tggtcgggtg tttgctggtg ccccagctg aagccaacaa gagttctgaa gatatccggt 180
gcaaattgcat ctgtccacct tatagaaaca tcagtgggca catttacaac cagaatgtat 240
cccagaagga ctgcaactgc ctgcacgtgg tggagcctcat gccagtgcct ggccatgacg 300
tggagggccta ctgcctgctg tgcgagtga ggtacgagga gcgcagnacc accaccatca 360
aggatcatcat tgtcatctac ctgtccgtgg tgggtgccct gttgctctac atggccttcc 420
tgatgctggt ggacctctg atccgaaagc cggatgcata yactgagcaa ctgcacaatg 480
aggaggagaa tgaggatgct cgtcttatgg cagcagctgc tgcaccctc gggggacccc 540
gagcaaacac agtcctggag cgtgtggaag gtgccagca gcggtggaag ctgcagggtgc 600
aggagcagcg gaagacagtc ttcgatcggc acaagatgct cagctagatg ggctggtgtg 660
gttgggtcaa ggccccaaca ccatggctgc cagcttcag gctggacaaa gcagggggct 720
acttctccct tccctcgggt ccagtcttcc ctttaaaagc ctgtggcatt tttcctcctt 780
ctccctaact ttagaaatgt tgtacttggc tattttgatt agggaaagagg gatgtggtct 840
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gggaatggag acattcgagg cgccctcagg agtggatgcg atctgtctct cctggctcca 960
ctcttgccgc cttccagctc tgagtcttgg gaatgttgtt acccttgga gataaagctg 1020
ggtcttcagg aactcagtg ctgggaggaa agcatggccc agcattcagc atgtgttctt 1080
ttctgcagtg gttctttatc accacctccc tcccagcccc agcgcctcag cccagcccc 1140
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tcagggtgca ctggaagctg gtgttcgctg tcccctgtgc acttctcgca ctggggcatg 1260
gagtgcccat gcatactctg ctgccggtcc cctcacctgc acttgagggg tctgggcagt 1320
ccctcctctc cccagtgtcc acagtcactg agccagacgg tcggttgga catgagactc 1380
gaggctgagc gtggatctga acaccacagc ccctgtactt ggggtgcctc ttgtccctga 1440
acttcgttgt accagtgcac ggagagaaaa ttttgcctc ttgtcttaga gttgtgtgta 1500

```

166

```
aatcaaggaa gccatcatta aattgtttta tttctctcaa aaaaaaaaaa aaaaaaccaa 1560
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
aaaaaaaaaa aaaaaaaaaa aangg 1645
```

```
<210> 219
<211> 478
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc feature
<222> (344)
<223> n equals a,t,g, or c
```

```
<220>
<221> misc feature
<222> (415)
<223> n equals a,t,g, or c
```

```
<220>
<221> misc feature
<222> (452)
<223> n equals a,t,g, or c
```

```
<220>
<221> misc feature
<222> (469)
<223> n equals a,t,g, or c
```

```
<400> 219
tcgacccacg cgtccgggga attcaaggag acggggggcga cgcggctgct ggcgcctcct 60
cgggtttggg gctgccgcca tcatgccggg gatagtggag ctgcctactc tggaggatct 120
gaaagtgcag gaggtgaaag tcagttcttc ggtgctcaaa gctgccgccc atcactatgg 180
agttcagtgt gacaagccca acaaggagtt catgctctgc cgctgggaag aaaaagaccc 240
ccggcggtgt ttagaggaag gcaagctcgt caacaaktgt gctctggayt tcttcaggca 300
gataaagctt tcaactgtgca gagcctttta cagactattg gacntgcac gactactccg 360
gcctgcagtg ttttcgtcgc tgccgcaaac agcaggccaa tttgacgatg tgtgnggggc 420
aactgggatg gtgcggctga actggggaaa angttccagt caccaaattg aaaacagt 478
```

```
<210> 220
<211> 832
<212> DNA
<213> Homo sapiens
```

```
<400> 220
atcttagtag agacaagggt tcaccatggt ggccaggctg gtctcgaact cctggcctca 60
ggtgatccac ctgccttggc ctcccaaagt gctccgatta cagggtgkgag ccacccggcc 120
cagcccctcc cttgtgtttc aaccaatcgg aagtgaattt aactagatgt agtaaccttt 180
tttttcttta cttctaaaaa agttacagtt tactaataaa gttaagtctg gttctgtcct 240
agaggaaata aattcactat taattcatgt cttaagttac ttgggttaaa acactttcag 300
ccaccagat taattaaagt ggagcagtggt agcccctggc tgggagatgg cctccagagg 360
```

```

agcagctgca gggcaygttc tgggcttagc gacagaggca agcaaggac tgggtgtctct 420
ggtgagaggt gggtttgatg tatctctgtc ctatgctggc ctctcttctc ctttataaaa 480
tcctctgtgg tcaactgact actgcgtatc gcagtggaaat aagactgcac agttgctggc 540
aggtgagttt aaagtcttaa tctatgcatt cagagaaaata tttttatatg ctttgtgtaa 600
tttataacaa ggattttttt tttagctttg ttaactgtga attcaccctt cctcctccac 660
tgcatattta aagcatgtgt tcacactgtg tgtaaacatt cactgaagat tttttctttg 720
tgcatgtgtg actgttcaaa cataacaagt attattaaaa ttaaatatta actgacaaaa 780
aaaaaaaaaa aaaactcgag gggggggccc gtaccaatt cgcccgaggt ag 832

```

<210> 221

<211> 1892

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1892)

<223> n equals a,t,g, or c

<400> 221

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aaaaaaaaa aaaaaaaaaa aaaaaaaaaa an

1892

<210> 222

<211> 868

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (23)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (45)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (829)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (860)

<223> n equals a,t,g, or c

<400> 222

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ttacttcata tccgggggaa tgtggctttg tgttcaccaa ggaggcctca cttgagatca 180
gggacatgct gctggccaat aaggtgccag ctgccgcccg tgctgggtgcc atagccccat 240
gtgaggtcac tgtgccagcc cagaacactg gtctggggcc cgagaagacc tccttcttcc 300
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tccgcaatgt tgccagcgta tgtctgcaga taggttaccc aactgtggca tcagtgtccc 600
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ttccacttgc tgaaaaggtc aaggccttct tggctgatcc atctgcattt gtggctgctg 720
ccctgtggc cgtgccacc actgctgcac ctgctgctgc tgcagcccca gccaaagttg 780
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<210> 223

<211> 1516

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1493)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1497)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1508)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1509)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1516)

<223> n equals a,t,g, or c

<400> 223

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cgatggggat ggaagaggag atgcctgtga tgatgacatg gatggagatg gaataaaaaa 180
cattctggac aactgccc aaatttccaa tcgtgaccaa cgggacaagg atgggtgatgg 240
tgtgggggat gcctgtgaca gttgtcctga tgtcagcaac cctaaccagt ctgatgtgga 300
taatgatctg gttggggact cctgtgacac caatcaggac agtgatggag atgggcacca 360
ggacagcaca gacaactgcc ccaccgtcat taacagtgcc cagctggaca ccgataagga 420
tggaatttgt gacgagtgtg atgatgatga tgacaatgat ggtatcccag acctggtgcc 480
ccctggacca gacaactgcc ggctgggtccc caaccagccc caggaggata gcaacagcga 540
cggagtggga gacatctgtg agtctgactt tgaccaggac cagggtcatcg atcggatcga 600
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cctggatcct gaaggggatg cccagatcga tcccactgg gtggctcctga accagggcat 720
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gggcccgnnc caattn 1516

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<210> 224

<211> 1306

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (148)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (887)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1242)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1264)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1303)

<223> n equals a,t,g, or c

<400> 224

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gctggacgag gtcattggctg ccgctgcnst tacaagcctg tccaccagcc ctctccttct 180
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ggccagtgc cagtcctctc cgtccacccc gtcaccccca ctgccccccg aggcagccca 360
ctttctgttt ggggagccca ccctgagaaa aaggaagagc ccggcccagg tcatgttcca 420
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ccgcctggtg cacctgggga ggcaggcaga gcctgatcag agtgatgggt aggaggactt 540
ctactacaca gagctggatg ttggtgtgga cacgtgacc gacgggctgt ccagcctgac 600

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171

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tccagtgtcc cccacggcct ccatgccgcc tgccttcccc cgcctggagc tgccagagct 660
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ccctgtcctg agcaccgttg ctaaccccca gtcctgtcac agtgaccgtg tctaccaggg 780
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<210> 225

<211> 584

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (486)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (542)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (562)

<223> n equals a,t,g, or c

<400> 225

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ggaacccag acccaagacc aaccgatgga ggaggaggag gttgagacgt tcgcctttca 120
ggcagaaaty gcscagttga tgcrytgat catcaayacy ttctactcga acaargagat 180
cttcttgccg gactgatctc caactcgtcc gacgctcygg acaaaatccg atacgagagc 240
ctgaccgacc ccagcaagct cgactcgggg aaggagctgc acattaacct catcccgaa 300
aagcaggacc ggaccctcac catcgtggga taccgggatc gcatgaccaa ggccgacctg 360
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gcgggagcag atatttcyat gattggccag ttcggggctcg ggttctattc ggctacttg 480
gtggcnagaa ggtgacggtg atcaccaagc acaacgatga cgagcattac gcctgggagt 540
cntccgcagg ggctcgttca angttccgca ttgacacagt gaac 584

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<210> 226

<211> 523

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature
 <222> (34)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (498)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (514)
 <223> n equals a,t,g, or c

<400> 226
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 atggtgacag acatccagac tgctgtaagg accaactcca cctttgttga agctttggtg 120
 gaccatgcc aagcacagtg tgatctcctg gggcccggca tggctgacat gtgcaagaac 180
 tatatcaacc agtattcgga cattgccgtc cagatgatga tgcacatgca acccaaagag 240
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 aaggacacgg tccaggcaaa gaccagtgtt agctgtggag atatgagagt tacgtggtg 420
 aaggaaagtg ccaagctcca ttggacaaca acaggactga ggaagaaata gtttcaggct 480
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<210> 227
 <211> 2377
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (2369)
 <223> n equals a,t,g, or c

<400> 227
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 ggtccaagtc caagtcctcg tcggtctcca gatctcggtc gcggtccagg tcccgggtctc 180
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aagggcccta agtagctcag atattaaagt agtattctca attaccaaatt gtttcatttg 960
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tgtaagtact tataacatgg tgtatctttt tgcttatgaa tattctgtat tataaccatt 2280
gtttctgtag ttttaattaaa acattttctt ggtgttagct tttctcagaa aaaaaaaaaa 2340
aaaaaaaaaa aaaaaaaaaa aaaaaaaang aaaaaag 2377

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<210> 228

<211> 463

<212> DNA

<213> Homo sapiens

<400> 228

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acaatatgac tctccttta cttcatcatg acttgaagac tcagaatatc ttattggaca 180
atgaatttca tgtaagatt gcagattttg gtttatcaaa gtggcgcatg atgtccctct 240
cacagtcacg aagtagcaaa tctgcaccag aaggaggac aattatctat atgccacctg 300
aaaactatga acctggacaa aaatcaaggg ccagtatcaa gcacgatata tatagctatg 360
cagttatcac atgggaagtg ktatccagaa aacagccttt tgaagatgtc accaatcctt 420
tcagataat gtatagtgtg tcacaaggac attggactgg tat 463

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<210> 229

<211> 1232

<212> DNA

<213> Homo sapiens

<400> 229

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caggtagagca tctgaacaag gggcagtcgg ccagggtggg cttgcgggag tccccacctt 60
gacctctctc ccttccagct gccacagacc cagaccaagc atggacgccg tggatgccac 120
catggagaaa ctccgggcac agtgccctgt ccggggggcc tcgggcatcc agggcctggc 180
caggtttttc cgccaactag accgggacgg gagcagatcc ctggacgctg atgagttccc 240

```

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gcaggggtctg gccaaactcg ggctgggtgct ggaccaggcg gaggcagagg gtgtgtgcag 300
gaagtgggac cgcaatggca gcgggacgct ggatctggag gagttccttc gggcgctgcg 360
gccccccatg tcccaggccc gggaggctgt catcgagct gcatttgcca agctggaccg 420
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cggcgtgagt gcctccatga acacggatga ggagttcgtg gccatgatga ccagtgcctg 660
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gacctgcccc ggtgtggagc gaggggcaca ggggcatcct aacctcagaa actgaaataa 1140
agcctttgaa aaaaaaatct gtaaaacatc aacccccaat cagaagatgg caaatgggga 1200
ataaaaatag caggtaacac gtcaaaaaaa aa 1232

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<210> 230

<211> 1063

<212> DNA

<213> Homo sapiens

<400> 230

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gctataggac aacagaactc tcaccaaagg accagacaca gtgggcacca tgggacagt 120
tcggctagcc aacgcagagg atgctcagga attcagtgat gtggagaggg ccattgagac 180
cctcatcaag aactttcacc agtactccgt ggagggtggg aaggagacgc tgaccccttc 240
tgagctacgg gacctgggtca cccagcagct gcccctctc atgccgagca actgtggcct 300
ggaagagaaa attggcaacc tgggcagctg caatgactct aaactggagt tcaggagttt 360
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ctgagaactc cctctggaat tcttgggggg tgttggggag agactgtggg cctggaaata 480
aaacttgtct cctctaccac caccctgtac cctagcctgc acctgtccwc atctctgcaa 540
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<210> 231

<211> 1063

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1056)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1061)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1063)

<223> n equals a,t,g, or c

<400> 231

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cctataatgc aagaaccaag gcgagtcacg ccctgtctgg gcaaaagagg agtaaagacc 300
cctcagctgc agcccggcag cgcattccta cccagggtcc gccgccagag ctttcccgcg 360
cggtcggata gttacactac tgtccgggac ttcctagccg tgccgcggac catctcaagt 420
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gagcgcaggc gcctacaaat cgaggacttc gaggctcgca tcgcgctgtt gccactgtta 720
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<210> 232

<211> 1474

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1337)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1359)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1377)

<223> n equals a,t,g, or c

<400> 232

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aggctctctt aagatgttca agggcccaag gccg 1474
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<210> 233

<211> 1782

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (8)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (34)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (591)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1760)

<223> n equals a,t,g, or c

<400> 233

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caaagcctgc tgggtgagca ccttgctcat tatactggwt ctgaatttac ctctttgaag 180
tttctagatg caccacttcc tgctcacagc ctggaattcg gttaacaagt cagtgtcaac 240
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aggaaggata aagcacatgt ttgtttctgc ttctgttttc tttttcttt ttttcasgaa 480
gccttatgga gaagtatgtt tctgctttct ttctgrgga agcctagytt ctgggccacg 540
ggactgatcc tgtctacatc ctctttccct ccattctcca tcgtgtctct nccccgtct 600
caccaccacc gtgcccctct ytgscacagc ttccctctt cccctgcagt gaggttcctg 660
cgcagcggca ctaagctcat ctccgcgcg aggcctagga agaaggaaagc tggcctgagc 720
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gagccacgca aggctgcacc tctgtgtgtt gggagacgat gatgatgtcc attgctgtgt 1680
gatggcttgg aatttaattt attaaagtca aattggagtt taacacacac aacacacac 1740
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<210> 234

<211> 2208

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1314)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2189)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2202)

<223> n equals a,t,g, or c

<400> 234

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ctccaacgtg cgcgtcataa aggacaagca gacccaactg aaccgcggct ttgccttcat 180
ccagctctcc accatcgagg cagcccagct gctgcagatc ctgcaggccc tgcaccacc 240
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<210> 235

<211> 2580

<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (1)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (3)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2558)
<223> n equals a,t,g, or c

<400> 235
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<210> 236

<211> 3008

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (3001)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3008)

<223> n equals a,t,g, or c

<400> 236

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<210> 237

<211> 877

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (834)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (854)

<223> n equals a,t,g, or c

<400> 237

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tggccctcta cttcagatta ctttctatga agacaaaaat tttcaaggcc gtcgctatga 480

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ctgtgattgc gactgtgcag atytccacac atacctaaagt cgctgcaact ccattaaagt 540
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tcacatgcga gagaccatcc tgtaagtgtc ggaggtgtct ggattttcta tgancctacc 840
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<210> 238

<211> 3039

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (170)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (177)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3039)

<223> n equals a,t,g, or c

<400> 238

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tggtcacacg ccaggggaaag attgtcctgg aggacggcac cctgcctgtn accgaangct 180
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<210> 239

<211> 1992

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (12)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (13)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (29)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (87)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1989)

<223> n equals a,t,g, or c

<400> 239

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tgggcgatga gctggagatg atccggccca gcgtctaccg caacgtggcg cgtcagctgc 180
acatctccct gcagtctgag cctgtggtga ccgatgcgtt cctggccgtg gctggccaca 240
tcttctctgc aggcattcacg tggggcaagg tgggtgccct gtatgcggtg gccgcggggc 300
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tgggggagtt cgtgcgcaag accctggcaa cctggctgcg gagacgcggc ggatggactg 420
atgtcctcaa gtgtgtggtc agcacagacc ctggcctccg ctccccactgg ctggtggctg 480
cactctgcag cttcggccgc ttctgaagg ctgccttctt cgtgctgctg ccagagagat 540
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caccgaaca catcttccct ctccccaccc gagcctggag cactctaacc ctcgagagacc 660
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cctgtccctc ccagtgacg catggcactc aggagataca ggctggacat ggggcagtcg 1740
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gggggtgggc atgtgccagg acaggagggg cccggcgga agccagcccc ggactcatcg 1860
tgacattgag atccccactg agggtagggg tggtaataaa cttctccaaa cgatgcgttg 1920
tcattttaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1980
aaaaaaaaanc cc 1992
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<210> 240

<211> 497
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (387)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (476)
<223> n equals a,t,g, or c

<400> 240
ggcagaactg tctgggacag acgctgcccg gatccctgcg gctgcctgca ctctggacca 60
cgagctctga gagcagcagg ttgagggccg gtgggcagca gctcggaggc tccgcgaggt 120
gcaggagacg caggcatggc cggtagctg actcctgagg aggaggccca gtacaaaaag 180
gctttctccg cggttgacac ggatggaaac ggcacccatca atgccagga gctgggcgcg 240
gcgctgaagg ccacgggcaa gaacctctcg gaggccagc taaggaaact catctccgag 300
gttgacrgcg acggcgacgg cgaaatcagc ttccaggagt tcctgacggc ggcrargaag 360
gccagggccg gcctggagga cctgcangtc gccttcgcg ccttcgacca ggatggcgac 420
ggccacatca ccgtggacga gctcaggcgg gccatkgcgg ggytggggma ccttcnagag 480
attgaccatt ttggagc 497

<210> 241
<211> 316
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (133)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (311)
<223> n equals a,t,g, or c

<400> 241
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tggtcaacga tagnaatctgt ggataatacg cacatttcgc cggaagtggg atccggttag 180
ccaraaagca ggcaggacgt gatggatatt gtatttatag agcaactttc ggtaatcacc 240
actattggtg tttagcactg ggrrcaacya tcgaacagaa gttagtgttc gatatcgaaa 300
tggcgtgggg ntaacc 316

<210> 242
<211> 829
<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (14)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (47)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (793)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (809)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (814)

<223> n equals a,t,g, or c

<400> 242

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gcaggtaccg gtcggaatt cccgggtcga cccacgcgtc cggaaagaaa agaagaaaag 120
aaaaaaagat cttcaaaagg gcagatgggt agaaggcata acctctgagg gttaccatta 180
ctattatgat ctatctcag gagcatctca gtgggagaaa cctgaaggat ttcaaggaga 240
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ccacccccaa actgtgtcct tttttttccc ataagtcttt tgttagaagg ctggatggag 420
atgaaatagt gatatctggc tgggtgcagt ggctcatgcc tgtaatccca gcactttggg 480

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aaccctatct ctctataaaa ctacaaaaaa attagccagg cgcagtcgca gttgcctgta 600
atcccagcta ctcaggaggc tgagtcaggg gaatcactgg gacctggggc ggcagagggt 660
aacagtgagc cgagattgca ccaccgcact ccagcctgga taacaaagta agactccgtc 720
tcaaaaaaaaa aaaaaaaaaa agggcggccg ctctagagga tccctcgagg ggcccaagct 780
tacgcgtgca tknaacgtca taggggctng ggcntttacc tttcccgtc 829

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<210> 243

<211> 838

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (32)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (51)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (822)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (832)

<223> n equals a,t,g, or c

<400> 243

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gccctttcca tccattaaaa atgtccaagt tccaagtgat atgtgccct aatatccacc 120
ttggatgttg gtgggttttt gaatttttgg gtggttaatc cagttttatt ttgaaaagac 180
gtacttgaat agttacagca tatgtttgaa caggaagtag gaacatgcat acacgaagaa 240
atgctaacgg aaggatttgt tatgtttagg atcttcctt ggaaactaaa aatagaatat 300
taatgacatt actgtttgta gaatgacata tgcagatttt ctcataagca gtcatttgt 360
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taattcgttg gttttgattc tcttattctc ttgtcttttc taaatgttaa caaaatatat 480
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gattcggatg cttttattat agtaactgaa gctaataatg ttttatgttt tgattttttg 600
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tacctgctt ataatactaa tgtttacaga tatgtttctg tttataacca tataatacat 720
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<210> 244

<211> 2853

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2665)

<223> n equals a,t,g, or c

<400> 244

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ccaaagctgc cttcaagcgc ttcaaaactc tacggcacc ccaacatcctg gcttacatcg 180
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tacaccagat cgtgaaagcc ctcagcttcc tggccaacga ctgcagcctc atccacaaca 360
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actacatgta ttcggcccag ggcaacggtg ggggamctcc ccgcaaggga tccccgagct 480
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gtcagcagac atgtggcgct tgggctgcct catttgggaa gtcttcaatg ggcccctacc 600
tcgggcagca gccctacgca accctgggaa gatcccaaa acgctgggtg cccattamtg 660
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cgctaaccgg ggaggggggc cggtaggggc gcctcgggty tcaaggcgcc gggaggggtct 2760
wgcgggccctg aaggtccctk ggtccgagcc acaagtcggg gcagaagtga ggccgagctc 2820
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<210> 245

<211> 1197

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (218)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1193)

<223> n equals a,t,g, or c

<400> 245

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tcccagggca tcatctaccg ggacctcaag cccgagaaca tcatgctcag cagccagggc 120
cacatcaaac tgaccgactt trgactctgc aaggagtcta tccatgaggg cggcgtcact 180
cacaccttct ggggcacat tgagtacatg gccctgnag attctggtgc gcagtggcca 240
caaccgggct gtggactggt ggagcctggg ggccctgatg tacgacatgc tctactggatc 300
ggcggcccttt accgcagaga accggaagaa aaccatggat aagatcatca ggggcaagct 360
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<210> 246

<211> 848

<212> DNA

<213> Homo sapiens

<400> 246

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ggcacgagga gagagacctg gcggccgggc agcatggcgg ggctggagct cttgtcggac 60
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ggcgtgttcg cgcaggctga cggctcggcc tacattgagc agggcaacac caaggcactg 180
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aaaaaaaaa

```

<210> 247

<211> 1336

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (26)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1336)

<223> n equals a,t,g, or c

<400> 247

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gaagatgaag aagatgatgt gtcagaggcg tctgaagtgc ccgagagtga ccgtcctgca 180
ggtgcccagc accaccagct taacggcgag cggggacctc agagtgccaa ggagagggtc 240
aaggagtgga cccctgcgag accgcaccag ggccaggatg aaggcggggg gccagccccg 300
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ktttttttaa taaaatttta aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1320
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<210> 248

<211> 1076

<212> DNA

<213> Homo sapiens

<400> 248

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<210> 249

<211> 2425

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (52)

<223> n equals a,t,g, or c

<400> 249

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<210> 250

<211> 1408

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (252)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1387)

<223> n equals a,t,g, or c

<400> 250

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cgagcccagc ctggccgtgt cagcgccggg ccgctgcaa cctcatcggg gaacacacgg 180
actacaacca gggcctggtg ctgcctatgg ctctggagct catgacggtg ctggtgggca 240
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gtgcagtggt ggtcagctca gtgcccctgg ggggtggcct gtccagctca gcatccttgg 480
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aacttgtgcc tccaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1380
aaaaaanaaa aagaaaaaaa aaaaaaaa 1408
```

<210> 251

<211> 494

<212> DNA

<213> Homo sapiens

<400> 251

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cttgtgtgcc tccagctctg ctgaggagta cgtgggcctg tctgcaaacc agtgtgccgt 120
gccagccaag gacagggtgg actgaggcta ccccatgtc accccaagg agtgcaacaa 180
ccggggctgc tgctttgact ccaggatccc tggagtgcct tgggtgttca agcccctgca 240
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cggagcaccc ttgccggct gtgattgctg ccaggcactg ttcattctcag cttttctgtc 360
cctttgtctc cggcaagcgc ttctgtgaa agttcatatc tggagcctga tgtcttaacg 420
aataaaggct ccatgctcca ccgaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480
aaaaaaaaaa aagg 494
```

<210> 252

<211> 2491

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (16)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2457)

<223> n equals a,t,g, or c

<400> 252

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<210> 253

<211> 1125

<212> DNA

<213> Homo sapiens

<400> 253

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attgctgccc tggagaagac tggaggaaac tcgaggaaga gggagaagcc gacaagtgct 180
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<210> 254

<211> 1409

<212> DNA

<213> Homo sapiens

<400> 254

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attaaagcag gcactgatca gggatatctc taagaggtaa ttcacttctt attcctttcc 1020
aataattatt acattctaaa ttttcatcta tgagaaataa caaacaagaa gggaatagaa 1080
ttaaattggg gtataatcta atcttcattg tttaaatggt ttgccttctc accattgaag 1140
ccatttttta tagcctcaga aagaggaaat aatgcctcca ccattttcta cctggtgact 1200
tgaaaattga acttttaagt taggaagaag ttagagtcag ggaacttgta taccactatc 1260

```

```
tatgcagcat tgttatagtc tgattatttc tgtgttttga atatgatttt cctaattgctc 1320
taaataaaat tttgttaaaa attaattttt tatttaataga tgtgcaaata ttgaatattt 1380
tagtatattt attaaaagtg gtagtcatt 1409
```

<210> 255

<211> 490

<212> DNA

<213> Homo sapiens

<400> 255

```
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tccgtggcct agcgcccccg tccccgccac ccgtgatcgt gcgccgaggc ccgcgagggg 120
tcgcccacca ggccgcctgg gttccacttc cagcaacagc tcctgcagca gtaccgagtg 180
ccccggggaa gccattcccc acccccagcgc tctcccgaag gctgaccgcg gtcattgggtg 240
ggccagcttc ttttccggga agtccaccct cccgttcatt gccacgggtg tggagtccgc 300
agagcactcg gaacctcccc aggcctccag cagcatgamc gcctgtggcc tggctcggga 360
agccccgagg aagcagcccg gcggtcagtc cagcamagcc agcgctgggc ccccgctctg 420
aactgagcgg ttaacaacaa gcccgaagcc tkcggaagcg ctagtycaac agagccctcc 480
gggccccttg 490
```

<210> 256

<211> 1233

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (45)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (602)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (931)

<223> n equals a,t,g, or c

<400> 256

```
ggcagagggt ggctcggggc tatgagaacg tgcccattcc ctgtntcacg gtgtggatgg 60
ggagccctgc cctgaggatt acaagtacat ctcagagaac tgcgagacgt ccaccatgaa 120
catcgatcgc aacatcaccg acctgcagca ctgcacgttt gtggacgact gctctagctc 180
caactgcctg tgcggccast tcagcatccg gtgctgggat gacaaggatg ggcgattgct 240
ccaggaattt aacaagattg agcctccgct gattttcgag tgtaaccagg cgtgctcatg 300
ctggagaaaac tgcaagaacc gggctcgtaca gagtggcatc aagggtgcgc tacagctcta 360
ccgaacagcc aagatgggct ggggggtccg cgccctgcag accatccac aggggacctt 420
catctgcgag tatgtcgggg agctgatctc tgatgctgag gctgatgtga gagaggatga 480
ttcttacctc ttcgacttag acaacaagga tggagagggt tactgcatag atgcccgtaa 540
ctatggcaac atcagccgct tcatcaacca cctgtgtgac cccaacatca ttcccgtccg 600
```

```

gntcttcatg ctgcaccaag acctgcgatt tccacgcata gccttcttca gttcccgaga 660
catccggact ggggaggagc tagggtttga ctatggcgac cgcttctggg acatcaaaaag 720
caaatatttc acctgccaat gtggctctga gaagtgcgaag cactcagccg aagccattgc 780
cctggagcag agccgtctgg cccgcctgga cccacaccct gagctgctgc ccgagctcgg 840
ctccctgccc cctgtcaaca catgagaacg gaccacaccc tctytcccca gcatggatgg 900
ccacagctca gccgcctcct ctgccaccag ntgctcgag cccatgcctg ggggtgctgc 960
catcttctct cccaccacc ctttcacaca ttctgacca gagatcccag ccaggccctg 1020
gaggtctgac agccctccc tcccagagct ggttctctcc tgggagggca acttcagggc 1080
tggccacccc ccgtgttccc catcctcagt tgaagtttga tgaattgaag tcgggcctct 1140
atgccaactg gttccttttg ttctcaataa atgttgggtt tggtaaaaaa aaaaaaaaaa 1200
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aac                                     1233

```

<210> 257

<211> 2404

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2372)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2385)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2395)

<223> n equals a,t,g, or c

<400> 257

```

cggacggtgg gacgggsaag tgggggtgaa aagcgcccg acctgcttgc ggtgtagtgg 60
gcggaccgcg cggctggagg tgtgaggatc cgaaccagg ggtggggggg ggaggcggct 120
cctgcgatcg aaggggactt gagactcacc ggccgcacgc catgagggcc ctgtgggtgc 180
tgggcctctg ctgctcctg ctgaccttcg ggtcggtcag agctgacgat gaagttgatg 240
tggttggtac agtagaagag gatctgggta aaagtagaga aggatcaagg acggatgatg 300
aagtagtaca gagagaggaa gaagctattc agttggatgg attaaatgca tcacaaataa 360
gagaacttag agagaagtcg gaaaagtgtt ccttccaagc cgaagttaac agaattgatg 420
aacttatcat caattcattg tataaaaata aagagatttt cctgagagaa ctgatttcaa 480
atgcttctga tgctttgatg aagataaggc taatatcact gactgatgaa aatgctcttt 540
ctggaaatga ggaactaaca gtcaaaatta agtgtgataa ggagaagaac ctgctgcatg 600
tcacagacac cgggttagga atgaccagag aagagttggg taaaacctt ggtaccatag 660
ccaaatctgg gacaagcgag tttttaaaca aaatgactga agcacaggaa gatggccagt 720
caacttctga attgattggc cagtttgggt tcggtttcta ttccgccttc cttgtagcag 780
ataaggttat tgtcacttca aaacacaaca acgataccca gcacatctgg gagtctgact 840
ccaatgaatt ttctgtaatt gctgacccaa gaggaacac tctaggacgg ggaacgacaa 900
ttacccttgt cttaaaagaa gaagcatctg attaccttga attggataca attaaaaatc 960
tcgtcaaaaa atattcacag ttcataaact ttcctattta tgtatggagc agcaagactg 1020
aaactgttga ggagcccatg gaggaagaag aagcagccaa agaagagaaa gaagaatctg 1080

```

```

atgatgaagc tgcagtagag gaagaagaag aagaaaagaa accaaagact aaaaaagttg 1140
aagaaacact ctaggacggg gaacgacaat tacccttgtc ttaaaagaag aagcatctga 1200
ttaccttgaa ttggatacaa ttaaaaatct cgtcaaaaaa tattcacagt tcataaactt 1260
tcctatttat gtatggagca gcaagactga aactgttgag gagcccatgg aggaagaaga 1320
agcagccaaa gaagagaaaag aagaatctga tgatgaagct gcagtagagg aagaagaaga 1380
agaaaagaaa ccaaagacta aaaaagttga aaaaactgtc tgggactggg aacttatgaa 1440
tgatatcaaa ccaatatggc agagaccatc aaaagaagta gaagaagatg aatacaaagc 1500
tttctacaaa tcattttcaa aggaaagtga tgaccccatg gcttatattc actttactgc 1560
tgaaggggaa gttaccttca aatcaatttt atttgtaccc acatctgctc cacgtggtct 1620
gtttgacgaa tatggatcta aaaagagcga ttacattaag ctctatgtgc gccgtgtatt 1680
catcacagac gacttccatg atatgatgcc taaatacctc aattttgtca aggggtgtgt 1740
ggactcagat gatctcccct tgaatgtttc ccgcgagact cttcagcaac ataaactgct 1800
taaggtgatt aggaagaagc ttgttcgtaa aacgctggac atgatcaaga agattgctga 1860
tgataaatac aatgatactt tttggaaaaga atttggtacc aacatcaagc ttggtgtgat 1920
tgaagaccac tcgaatcgaa cacgtcttgc taaacttctt aggttccagt cttctcatca 1980
tccaactgac attactagcc tagaccagta tgtggaaaaga atgaaggaaa aacaagacaa 2040
aatctacttc atggctgggt ccagcagaaa agaggctgaa tcttctccat ttggtgagcg 2100
acttctgaaa aagggtctatg aagttattta cctcacagaa cctgtggatg aatactgtat 2160
tcaggccctt cccgaatttg atgggaagag gttccagaat gttgccaagg aaggagtga 2220
gttcgatgaa agtgagaaaa ctaaggagag tcgtgaagca gttgagaaag aatttgagcc 2280
tctgctgaat tggatgaaag ataaagccct taaggcmag rtactgtggg aaattttacc 2340
aatttgtggg aaatattagt gtccggcatt tnaggggaaa gttntttttt ggggnaacca 2400
aatt 2404

```

<210> 258

<211> 2092

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (27)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (60)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2069)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2071)

<223> n equals a,t,g, or c

<400> 258

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tatncaacaa ctaaaacgac tcactanagg naaaagcagg aacgcctgca ggaaaccggn 60
ccggaattcc cgggtcgacc cacgcgtccg ctgccgctcc ctttgccgcc gccttagccc 120
gggacccgaa cccagcctct cccctacccc aacaccggcc cgggctccac cgaggccccg 180
gtcccccagc ccgtctcgcc gccgccatgg cggaccctaa atacgccgac cttcccgga 240
ttgccaggaa tgagccagat gtttatgaaa ctacgcacct acctgaggat gatcaagcgg 300
agttcgatgc ggaggagctg acaagcacia gtgtggaaca catcattgtc aatcctaattg 360
ctgcctatga caagtccaag gacaagagag tggggacaaa gggacttgat ttctcagatc 420
gtattggaia aaccaagagg acaggatatg aatctggaga atatgagatg cttggagagg 480
gtctgggagt gaaggagaca ccccagcaaa agtaccagcg cctactgcat gaggtccaag 540
agctgacaac tgaagttgaa aaaatcaaga cgacagtga ggaagtcagcc acagaggaga 600
agctgacccc tgtgttgctg gctaaacagc tggcagccct gaagcagcag ctggttgctt 660
ccacactgga gaagctgctg ggaccagatg ctgcaatcaa ccttaccgac cccgatggcg 720
ccctggctaa ggcgcctacta ctgcagctgg aagcaacaaa gaacagcaaa gggggatcag 780
ggggaaaaac cactgggacc ccccagata gcagccttgt cacttatgaa ctacattctc 840
ggcctgagca ggacaagttc tctcaagctg ccaaagtcgc agaacttgaa aagcgctga 900
cagagctgga gacagctgta cgttgtgatc aggatgctca gaatccccct tctgcaggtc 960
tacagggagc ctgtctcatg gagactgtag agctgttgca agcaaagggt agcgccctag 1020
accttgcatg tttggatcaa gtggaggctc ggctacagag tgcctctgga aaggtgaacg 1080
agattgcaaa gcataaagcc tctgtagaag atgcagatac acaaagcaag gtgcaccagc 1140
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gacttgctac catcaagcag ctgcacgagc aagccatgca gtttggtcag ctctgacac 1260
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acccctcccc tgatgaatac agagtggtag ctagggggtg gttatcatca gaagggtggtc 1620
tcccctcagg cctgggggat aaggacgtgg gccagccac atgccaactc atgtccaata 1680
ctgctttgcc tgggtgtggg aaggattggg tctgtgcccc caacacagct tctgtggctg 1740
actgtaatac tgtacaactg tttctgacca ttaaagtctg ttgtactctg tgtggcctct 1800
gctgtgtttc ctggggagga agcagcacta ggatatagat attcattcgt cataacaggc 1860
aatctaagcc actctatact acaagagatg gatttaaatt gtaacctgtt cttaccaaaag 1920
aactaaataa aaaatgagta cagagccaga gccagagttt caaaatattc tcatctgtta 1980
aattaagagt gtctcccata gaaaagcagt ggaggcccca cagggcaagt acaaaacaga 2040
attaaaactc aaaaaaaaaa aaaaaaaanc ncaagggggg gcccggtccc ca 2092
```

<210> 259

<211> 387

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (377)

<223> n equals a,t,g, or c

<400> 259

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aattcggcac gaggttcat tctctgacct ttctctctcc tcatttcggt gcatgtcctt 60
tctgcagctg cctttcagca caggtggctg ccccccaggg ccaccgcttc tttcttgatc 120
ctctttcctt aacagtgact tgggcttgag tctggcaagg aaccttgctt ttagcttcac 180
caccaaggag agagaccaa agcctctgat ttttaatttc cataaaatgt tagaagtata 240
tatatacata tatataattt tttaaatttt tgagtctttg atatgtctaa aatcattcct 300
ctgcctgaag cctkagtga cecatgarga actgtgttca ttaagtgtta ttaatgttga 360
actgaaaaaa aaaaacnggg ggggccg                                     387
```

<210> 260

<211> 3712

<212> DNA

<213> Homo sapiens

<400> 260

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tatccccgac gaccggatcc tgaggaggca gctgcggtgg cagctgctga gttctcggtg 60
aaggtatttc atttctcctg tccccctccc tccccacccc atctattaat attattcttt 120
tgaagattct tcgttgtaaa gccgccaaag tggagagtgc gattgcagaa gggggtgctt 180
ctcgtttcag tgcttcttcg ggcggaggag gaagttagggg tgcacctcag cactatccca 240
agactgctgg caacagcgag ttcctgggga aaacccagg gcaaacgct cagaaatgga 300
ttcctgcacg aagcactaga cgagatgaca actccgcagc aaacaactcc gcaaacgaaa 360
aagaacgaca tgatgcaatc ttcaggaaag taagaggcat actaaataag cttaactcctg 420
aaaagtttga caagctatgc cttgagctcc tcaatgtggg tgtagagtct aaactcatcc 480
ttaaaggggt catactgctg attgtggaca aagccctaga agagccaaag tatagctcac 540
tgtatgctca gctatgtctg cgattggcag aagatgcacc aaactttgat ggcccagcag 600
cagagggtca accaggacag aagcaaagca ccacattcag acgcctccta atttccaaat 660
tacaagatga atttgaaaac cgaactagaa atggtgatgt ctatgataag cgtgaaaatc 720
ccctcctccc cgaggaggag gaacagagag ccattgctaa gatcaagatg ttgggaaaca 780
tcaaattcat tggagagctt ggcaagcttg atcttattca cgaatctatc cttcataagt 840
gcataaaaac acttttgaa aagaagaaga gagtccaact caaagatatg ggagaggatt 900
tgagtgacct ctgtcagata atgaggacag tgggacctag attagaccat gaacgagcca 960
agtccttaat ggatcagtac tttgcccga tgtgctcctt gatgttaagt aaggaattgc 1020
cagcaaggat tcgtttcctg ctgcaggata ccgtagagtt gcgagaacac cattgggttc 1080
ctcgcaaggc tttcttgac aatggaccaa agacgatcaa tcaaattcgt caagatgcag 1140
taaaagatct aggggtgttt attcctgctc ctatggctca agggatgaga agtgacttct 1200
ttctggaggg accgttcatg ccacccagga tgaaaatgga tagggaccca cttggaggac 1260
ttgctgatat gtttgacaaa atgccaggta gcggaattgg tactgggtcca ggagttatcc 1320
aggatagatt ttaccccacc atgggacgtc atcgttcaaa tcaactcttc aatggccatg 1380
ggggacacat catgcctccc acacaatcgc agtttgaga gatgggaggc aagtttatga 1440
aaagccaggg gctaagccag ctctaccata accagagtca gggactctta tcccagctgc 1500
aaggacagtc gaaggatatg ccacctcggt tttctaagaa aggacagctt aatgcagatg 1560
agattagcct gaggcctgct cagtcgttcc taatgaataa aaatcaagtg ccaaagcttc 1620
agccccagat aactatgatt cctcctagtg cacaaccacc acgcactcaa acaccacctc 1680
tgggacagac acctcagctt ggtctcaaaa ctaatccacc acttatccag gaaaagcctg 1740
ccaagaccag caaaaagcca ccaccgtcaa aggaagaact ccttaaaacta actgaaactg 1800
ttgtgactga atatctaaat agtggaatg caaatgaggc tgtcaatggt gtaagagaaa 1860
tgagggctcc taaacacttt ctctctgaga tgttaagcaa agtaatcatc ctgtcactag 1920
```

```

atagaagcga tgaagataaa gaaaaagcaa gttctttgat cagtttactc aaacaggaag 1980
ggatagccac aagtgacaac ttcattgcagg ctttcctgaa tgtattggac cagtgtccca 2040
aactggaggt tgacatccct ttggtgaaat cctatttagc acagtttgca gctcgtgcc 2100
tcatttcaga gctggtgagc atttcagaac tagctcaacc actagaaagt ggcacccatt 2160
ttctctctt cctactttgt cttcagcagt tagctaaatt acaagatcga gaatggtaa 2220
cagaactttt tcaacaaagc aagggtcaata tgcagaaaat gctcccagaa attgatcaga 2280
ataaggaccg catggttgag attttggaag gaaagggact gagtttctta tccccactcc 2340
tcaaattgga gaaggaactg ttgaagcaaa taaagttgga tccatcccct caaacatat 2400
ataaatggat taaagataac atctctccca aacttcattg agataaagga tttgtgaaca 2460
tcttaatgac tagcttctta cagtacattt ctagtgaagt aaaccccccc agcgtatgaa 2520
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ctttcaagcc agtaatgcag aaatttcttc atgatcacgt tgatctacaa gtcagtgcc 2640
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tttttgagca cttctatgac atggaaatta ttgaagaaga agctttcttg gcttggaag 2760
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gttaggattt ccttctgcat aagggttttt ttagtgtaa tgtcttaatc atagtctacc 3060
atcaaatatt ttaggagtat ctttaatggt tagatagtat attagcagca tgcaataatt 3120
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gtaatgggct ttatgtgcta gattttaata tccttgagcc tgggcaagtg cacaagtctt 3420
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tatagtattg aaattaagtc tacttaattt atcaagtcac gtccatgccc tgattttata 3600
tacttgtatc tatcaataaa cattgtgata cttgaaaaaa aaaaaaaaaa aaaaaaaaaa 3660
aaaaaaaaaa aaaaaaaaaa aaaaaaaagg aggaaaaaaa aaaaaaaaaa aa 3712

```

<210> 261

<211> 897

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (22)

<223> n equals a,t,g, or c

<400> 261

```

agagctggaa ggaggaggag angaaacctc accttcaggg caaaccaggg agacccttgt 60
ccccggccaa tgtccctgct ctgcctggcg agacgggtgac ctccccagtc aggtgcacc 120
ccgactacct ctccccggag gagatacaga ggcagctgca ggacatcgag aggcggctgg 180
acgccctgga gctccgcggc gtggagctgg agaagcgact gcgggcggcc gagggagatg 240
acgctgagga tagcctcatg gtggactggt tctggctcat tcacgagaag cagcttctgc 300
tgagacagga gtcagagctg atgtacaagt ccaaggccca gcgtctggag gagcagcagc 360
tgagacatga gggcgagctg cgccggctca tggccaagcc cgaggctctg aagtcaactgc 420
aggagcggcg gcgggagcag gagctgctgg agcartacgt gagcaccgtg aacgaccgca 480
rtgacatcgt ggactcgcctk gacgaggacc ggctccsgga acaagaggag gatcagatgc 540

```

```

tgcgggacat gattgagaag ctgggcctcc agaggaagaa gtccaagttc cgcttgtcca 600
agatctgggtc accaaaaaagc aaaagcagcc cctcccagta gtagccagta gggccgtggg 660
ctcgggccggg acctggcatc cggacttgga ctcggggcca tgggcttggc ccggaccggg 720
aaccgggact tgtactcggg gccgtgggct cggcccgga cgggcattcg gacttggact 780
cggaagggc ctctgtccc tacaaggggc atgtggacag cagggacctg cgctaccgtc 840
tgtgtgtctca ataaagaaac cgaccacatg gaaaaaaaaa aaamaaaaaa aaaaaaa 897

```

<210> 262

<211> 1905

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1266)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1791)

<223> n equals a,t,g, or c

<400> 262

```

gctgtgatag cgcgtgagga ggcagaggcc tctgggggtg gatcgcgggc cgtaagtggc 60
tgtggagctg gggtcactgc gcgtggggac catggcctcg gagaagccgc tggcggcagt 120
cacttgtaca gcgccgttca acatcgcggt catcaagtac tggggcaagc gcgatgaaga 180
gctggttctg cccatcaact cctccctgag cgtcactctg caccaggacc agttaaaaac 240
caccacaaca gccgtcatca gcaaggactt caccgaggac cggatttggc tgaatggccg 300
ggaggaggat gtggggcagc cgmggctgca ggctgcctg cgggagatcc gctgcctggc 360
ccggaagcgg aggaactcac gggatgggga cccgctgccc tccagcctca gctgcaaggt 420
gcacgtggca tcggtgaaca acttccccac ggtgcggggc ctggcctcct cagcggcggg 480
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tgggtgtggc tggaatggtg gcaggagtgg gcaccagtgc ggccccggtg gccatgggga 1860
ataaaccagc attgctgcca aaaaaaaaaa aaaaaaaaaa aaaaaa 1905

<210> 263

<211> 1424

<212> DNA

<213> Homo sapiens

<400> 263

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gtgactgttt gattttaaaa agtgtgactg tcagttgtat ctgttgcttt tctcaatgat 180
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tgcatgtatg ttcccatgta gtaagtcatt tttagtttg ttgtgaaaaa accctgggct 1320
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<210> 264

<211> 1287

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (111)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (889)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1196)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1229)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1284)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1287)
<223> n equals a,t,g, or c

<400> 264
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ccgtcccgcg gccccagcc gcccccaacc ctgccccacg ggccccggcg catgagttag 180
ctggagcaac tgagacagga ggccgagcag ctccggaacc agatccggga tgcccgaaaa 240
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gcctacgcgc cctcaggga ctttgtggcc tgtgggggggt tggacaacat ctgctccatc 540
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ccacctgtgc cctgtgggac attgagacag gccagcagac agtgggtttt gctggacaca 720
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tccctgccct tccaaccaag ttngtn 1287

<210> 265
<211> 991
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature

<222> (421)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (966)

<223> n equals a,t,g, or c

<400> 265

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ccctggagct cttccgaacc aaggtgaatg cgctcactta tggggagggtg ctgcggctgc 180
ggcagactga acggctgcac caggagggca cactggctcc ccctatactg gagctgcggg 240
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caaggactgc ccccatgtcc gggagaaggg ctccgggaag cagaacaagg acctctatga 540
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ccatgggcca cagctgcggc cactgcagca gccatgaagg gcagtgggta gaggagtgc 900
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aaaaanaaaa aaaaaaaaaa aaaaaaaaaa a 991
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<210> 266

<211> 2320

<212> DNA

<213> Homo sapiens

<400> 266

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cagcaccctt gcctccttgg aagtccctt ccagctccca gcctctgccc caggttccgg 780
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<210> 267

<211> 423

<212> DNA

<213> Homo sapiens

<400> 267

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acagcaaaact gtcattggcca ttgctacaaa gattgcccta cagatgaact gcaagatggg 120
aggrgagctc tggagggttg acatccccct gaagctcgtg atgatcgttg gcatcgattg 180
tkacctgac atgacagctg ggcggaggtc aatcgagga tttgttgcca gcatcaatga 240
agggatgacc cgctggttct cagctgcat atttcaggat agaggacagg agctggtaga 300
tgggctcaaa gtctgcctgc aagcggtctt gagggcttgg aatagctgca atgagtacat 360
gccagccgg atcatcgtgt accgsgtggc gtaggagacg gccagytgaa aacactgggt 420
act 423
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<210> 268

<211> 1846

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1776)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1816)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1832)

<223> n equals a,t,g, or c

<400> 268

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tcactcagag gaaaaatgaa aaggaacaag aaagaagatt gcagcaggca gtgttaagca 180
gacagatgcc gtctgaaagc ttggacccag cgttcagtcc tcggatgccg tcctctgggt 240
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tagccctgag gtagttcatg aaaatgctgt gcactncatt ccatgggaat gaaatgttgg 1800
aaagctgatc ttttcnggat ataaaatggt gnatgatgaa aaaaaa 1846
```

<210> 269

<211> 601

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (536)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (556)

<223> n equals a,t,g, or c

<400> 269

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gtctcatact ctacaccagt attgctgtcc tactcaggtc cttgactcca tgaagcttac 180
cccctcaggc aggctggcag agagcaggga agaggaggag gaggaggaga ctgagggaaga 240
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tcggttaactg agaggacaag ggccattttc tatgcagaag caaaagcctt aaccagsccc 360
tccttcccc caccacccc cccgcagatt cccccatggg accctgtccc ctgcttcagg 420
aaccagatgg gcaagcatcg tgccccctcc tccccccacc ttcttcttgg aattccccatc 480
cccactgctg tctcctctgg actccagccc ctgaattaaa gaaactggag ccctangtcc 540
gactaaaatt tggganaagc aaacttgagc ttggacttgg aactggatcc tcccgtaccc 600
g 601
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<210> 270

<211> 880

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (876)

<223> n equals a,t,g, or c

<400> 270

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caagaaacac tgattttctt tcaggagagc ttcatgtgtt catttatctc caccacagca 720
gattttaaga aattataata tgtaatatct gatattctata aagagtatat ctaacgtgaa 780
taaattatga agcatactaa tgagtaccta tgaccataaa cacatatata ttaaaacatt 840
ttaaatacca aaaaaaaaaa aaaaaaaaaa aaaaanaaaa 880
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<210> 271

<211> 2484

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (194)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (623)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2396)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2484)

<223> n equals a,t,g, or c

<400> 271

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cgatcaagtt ccttcccatt tctccatctg ggggacctg aacgtgcaca tcctcagaga 180
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gagtcttgtc catgtgaagg gcgccaatgc cggggtccaa accttccttg gaattccatt 780
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```
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```

<210> 272

<211> 751

<212> DNA

<213> Homo sapiens

<400> 272

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gccttgtttg actgcraccg ccctgtgsg cagaagtctt gtgacctcct tctcttcctg 180
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caggagcctg aggtgtgtct ggccatgctc aggtccctag acctggaggg cctgcggagc 360
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ctggccacgg gaggttcct gcagggggac gaggccgact gctactgagc agaaccagag 480
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caaggtcaag aaatcccaca gtttgatgta ttaaagaaat gacttatctt tactcaaaat 660
aaatggcatt gaagtcttct ttttaaccctt tatgagttaa ttttaataata atgatctgag 720
acaaaaaaaa aaaaaaaaaa aaaaaaaaaa a 751
```

<210> 273

<211> 3309

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (3279)

<223> n equals a,t,g, or c

<400> 273

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aactgggccc atgtggtgtg acatccccac cagcctcaga tgagacgggc caggacgccc 180
agccacagca agcctgtcc ctttgccgga tccccaaaca ctagagaagc tctcctaacc 240
caaggcggag aatgaagggt gtggcggcag aggaggaggg cagcagctga gaggccaggg 300
acagggtgcc tcgccaagct gtctgaggtc tgtcccaggt ggcccagggt gtgcaggtag 360
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gagcttttag gtgttgagat ggggcagctc tgaatcctag accctggaat agcctgtccc 480
ttttctctgg gtctcgtggt ggagccatga tctgggctgc tctcttgggg acactgggtg 540
gtggttacac agttgacctc tgctggctc ccccttggtg caactcctgc ctccatcccc 600
```

```

cttgctgggg tccccctc cacttgaggg cgcctgaggg ccaggarcag caggcaagga 660
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cctgcccaga ccaacagaga gagctgtccc tgagaccccg gagagaagca gctgccgaaa 780
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caagtacact ccacacatgc ataaaggaaa tcaaatgtta tttttaagaa aatggaaaat 3240
aaaaacttta taaacaccaa aaaaaaaaaa aaaaaccng gggggggggc ggtaaccat 3300
ttcgctaa
3309

```

<210> 274

<211> 843

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (780)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (833)

<223> n equals a,t,g, or c

<400> 274

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cactcccacg accagtgacc aggagttaaa ctttgggatg tgcccgtgat gttggaccac 180
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tcccgggtgcc gagcggcggc gttttttctt tcattgtttc tctgcctttt tgtggtgttc 360
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gactacagtg ccgctgttat ctatgacttt ctggctgtgg atgatataaa cggggacagg 480
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cccagccaag aggcagttag gcaccttctg cctgcatcct ggtgggcaga cccagttcct 720
tcattgcagt caactgtgtc acaggggaaa ccttggaac cacagccagc agttcagggn 780
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tgt 843
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<210> 275

<211> 2028

<212> DNA

<213> Homo sapiens

<400> 275

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ttgaacctct ttatagcatt gatactaggt gaacagaaat tacctgacta ataatttgtc 180
taacatcata tatcagaatt ttattgtata tgatgaacaa aacttaaaat tttttaaat 240
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taaaaactgt aagaataatt tagcagaaat agaaccagaa tgtagaagag tagtcatgta 360
acagcagtaa taacatactt cagcttccat ataggaatag aagtggtaga gccaaaagtg 420
atthaggaag agttataagg tacagggtga gtatcccttt tccaaaaatg cttgggacaa 480
gaagtatttc agatttcata atttttttca aagtttgga tatttgcatt atacttacca 540
gttgggcac ccaaatctga aatctgaaat gttccatgag catttccttt gagtgcacg 600
ttggcactca aaaaggttca acattgagtc cacttaacac ttaggtgtta gaagacctaa 660
ctttctgtaa caattaacct tatactttgt ttgtcatcga atatttgtt aatgcacgtc 720
aggtaatggt ctgtattgtg atagcttcaa ggtggaacat actgtaactc ccagatgcta 780
ggaagttagt ctaataattc actgcagaaa attgattaag tggctgtcct ttaattaaag 840
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acaggatttt aaacatgggt tgggtattct aagccttttt tttaaaaaaa gagatctttt 1920
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aaactttgat taagctgaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 2028
```

<210> 276

<211> 1455

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (759)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1408)

<223> n equals a,t,g, or c

<400> 276

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agcgggacta tgatctcctg gtggtcggcg ggggatctgg tggcctggct tgtgccaagg 180
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gagtcaccga caccagaagt ctgaatttgg agaaggctgg ggtagatact agccccgaca 1020
```

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tggtctggac agatgcatcc cagtgttatg taaagatggt gtgcctgagg gagccccac 1380
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ctggggacaa gtgtg                                     1455

```

<210> 277

<211> 1923

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1814)

<223> n equals a,t,g, or c

<400> 277

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cgcggtcttct gtgggcccga accttaaaga tagccgcaat ggctgaaaat ggtgataatg 180
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aggctgggct ttgnatattt acacaggaaa gttgggtaac actagaaata attacttggt 1860

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215

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gga 1923

<210> 278

<211> 1380

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1293)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1297)

<223> n equals a,t,g, or c

<400> 278

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aattaaattt taaggagatt cttatctaata aacttttgtg gtgcttttgg atacaggctg 1260
aggctttact cctacactgg tgctgttaat ttncacnttt caggggatgt ctgctcggct 1320
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<210> 279

<211> 1018

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (818)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1017)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1018)

<223> n equals a,t,g, or c

<400> 279

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gcgctagcgc agctggttgg ccagcgcgcc asatgctgcc tggcaggggc ccgcgcccgt 120
ttcgcgctcg gcttgtcggg cgggagctcg tctcgatgct agcccgcgag ctaccgcgcg 180
ccgtcgcccc tgccgggcca gctagcttag cgcgctggac gctgggcttc tgcgacgagc 240
gcctcgtgcc cttcgatcac gccgagagca cgtacggcct ctaccggacg catcttctct 300
ccagactgcc gatcccagaa agccaggtga tcaccattaa ccccgagctg cctgtggagg 360
aggcggctga ggactacgcc aagaagctga gacaggcatt ccaaggggac tccatcccgg 420
ttttcgacct gctgatcctg ggggtgggcc ccgatggtca cacctgtca ctcttcccag 480
accaccccct cctacaggag cgggagaaga ttgtggctcc catcagtgc tccccgaagc 540
caccgccaca gcgtgtgacc ctcacrtac ctgtcctgaa tgcagcacga actgtcatct 600
ttgtggcaac tggagaaggc aaggcagctg ttctgaagcg cattttggag gaccaggagg 660
aaaacccgct gcccgccgcc ctggtccagc cccacaccgg gaaactgtgc tggttcttgg 720
acgaggcggc cgcccgcctc ctgaccgtgc ccttcgagaa gcattccact ttgtagctgg 780
ccagagggac gccgcagctg ggaccaggca cgcgccnat ggggctgggc ccctgctggc 840
cgccactctc cgggctctcc ttcaaaaag ccacgtcgtg ctgctgctgg aagccaacag 900
ctccggccag cagccctacc cggggctcaa cacacaggct gtggctctgg acatccggat 960
attaaaagga gcgttgctgg aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaann 1018
```

<210> 280

<211> 1192

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1105)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1130)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1154)

<223> n equals a,t,g, or c

<400> 280

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tccgggaatt cccgggtcga cccacgcgtc cgctctgttt atatagcagg tgtcacaact 60
aacttgtctt tagccttgggt gctttgatcc ttctatatatt tgacccca ggtgtggtcc 120
ggtttactta atcaggacat gggcctaaga acaaaccttt tcccttcatg ataacatcca 180
tagacaactt attagaaggg actagagttt ttgcaaattt ccctgctgga tggggcctat 240
agctatactt agtatatgcc taaacatggt aattggatag taaatggttt tctagtcca 300
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atcctgtacc aaatggggaa gaattaggaa ataatcatgt tgtctaattg tactctggat 420
tcagggcagc aactgccatt taaatgttgt cttgttcatt tctaaatctg ttccatgaag 480
tttaggtttt ccctgaaact aagtgaatt atttccaaaa tgaaacaggc ttctcaggga 540
catatccact tcttcccagt ctgcctttgg attaaagcac caagcagaga ccacattaat 600
tccctttgct atactgtgat ccttagtatg ttaattctta agaaaccaac atatcactga 660
aagaaggctg gcagaacgca agtgcatgtt ttcactgtgg gaagaaagat caagtacgt 720
attatttttt cctggttggt acttaattggg ctgagtaaaa agcttgaaaa ctcagacttt 780
cggctcttgg tctgccactc attggttatg aggaggccca gagcaggtaa gttcaccttc 840
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acaccagcag tagatacaac tatgatgaca ttccatgagt tgggtatttt agttctaact 960
gctaaatttg ttctctttac gggacagatt tctaataaag tgcttgggtc taaaatacat 1020
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ttatttttaa atttttaata ctttnggtac tccaattgtc cagtgttccn tgggtgttgt 1140
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```

<210> 281

<211> 1755

<212> DNA

<213> Homo sapiens

<400> 281

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agtcgtctat aaaaactcat ctctgcgcgt ctcttcgccca cattcgcttc ctgctttcgg 180
tgtgtctgtt gtgtcttgtt gcgggcaccg cagtcgccgt gaagatggcg tctaccagcc 240
gtttggatgc tcttccaaga gtcacatgtc caaaccatcc agatgcgatt ttagtggagg 300
actacagagc cgggtgatatg atctgtcctg aatgtggctt ggttgtagggt gaccgggtta 360
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gagttggaga ttctcagaat cctcttctga gtgatggaga tttgtctacc atgattggca 480
agggcacagg agctgcaagt tttgacgaat ttggcaattc taagtaccag aatcggagaa 540
caatgagcag ttctgatcgg gcaatgatga atgcattcaa agaaatcact accatggcag 600
acagaatcaa tctacctcga aatatagttg atcgaacaaa taatttatcc aagcaagtat 660
atgaacagaa gagcctgaag ggaagagcta atgatgctat agcttctgct tgtctctata 720
ttgcctgtag acaagaaggg gttcctagga catttaaaga aatatgtgcc gtatcacgaa 780
tttctaagaa agaaattggt cgggtgttta aacttatttt gaaagcgcta gaaaccagt 840
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aacaagtaca gatggcagct acacatatag cccgtaaagc tgtggaattg gacttgggtc 960
ctgggaggag ccccatctct gtggcagcgg cagctattta catggcctca caggcatcag 1020
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gacagtccta tagactgatc tatcctcgag cccagatctt gtttctaca gacttcaaat 1140
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tgaatacaaa actttgcctg ttgtacatag cctatacaaa atgctgggtt gagcctttca 1260
tgaggaaaaa caaaagacat ggtacgcatt ccagggtgta atactattgc ttggcattct 1320
gtatgtatat actagtgaat catatttaat gatttaaat tcttatcaaa tttcttttgt 1380

```

```

agcaatctag gaaactgtat ttggaagat atttgaaatt atgtaattct tgaataaaac 1440
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ataatgcaaa tcattgcagc taataaagct gatagacttt atttccatta cttatatata 1560
catagttttt tattttaata aatttatgga aagagcaaaa gcttttgaga accattgtta 1620
acatcaacat catagtttcc agtttgaaag gatgtgtatg tgagatttat tatgtatatt 1680
attaacaag aagtgatgag cttggccttg aaaggcacca gcttgagaga cattaataatg 1740
ttctaagtaa aaaaa 1755

```

<210> 282

<211> 1093

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (90)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (970)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1081)

<223> n equals a,t,g, or c

<400> 282

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gcctccgcgg atccggggccc gctcggcccn tcccatggaa ggtgctcggg tcttcggggc 120
actgggtccc atcgggtccct cctcacctgg gctcaccctc ggggggtctg cctgagcgca 180
gcaccggctc agcaacaagc tgctggcttg gagcggcgtc ctcgagtggc aggagaagcg 240
cagaccctac tctgactcca ctgcaaagct gaagcggacc ctgccctgcc aagcctacgt 300
gaaccaaggc gagaacctgg agaccgacca gtggccgcag aagctgatca tgcagctgat 360
ccctcagcag ctgctgacca ccctggggccc cctgttccgg aactcccagt tggcacagtt 420
ccacttcacc aacagagact gcgactcgct caaggggctc tgccgcacat tgggcaacgg 480
cttcgcgggc tgcagtctgt tccccacat ctccccctgt gaggtgcgcg tgctcatgct 540
cctgtactcg tccaagaaga agatcttcat gggcctcatc ccctacgacc agagcggcct 600
cgtcagtgcc atccggcagg tcatcaccac ccgcaagcag gcagtgggac ctggtggtgt 660
caactcaggc ccagtccaga tctcaacaa caagtttctg gcattggagt gtgtcatgga 720
gtggcaggag cccaggcctg agcccaacag tcggtccaag aggtggctgc catcccacgt 780
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tggtctcgcn ggctgcgtgc acttttctta caaagcatcg tgtgagatcc gcgtgcttat 1020
gtcctgttac tcttcagaga agaaaatytt cattggcytc atcccccatg accagggcaa 1080
ntttgtcaa agg 1093

```

<210> 283

<211> 1556

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1324)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1339)

<223> n equals a,t,g, or c

<400> 283

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ggcacgaggg gaatcctcca cgtggctgtc ccagcacgag gaacccatgc acagtgtgtc 60
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agacttgaga gagttcacat tccactgtca gcaccagcct cagcaactgt gcagagacct 180
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cccttggtgg cttctgttcc ttgtcccctc ggcttctctt cgcagccatc aggactaggt 300
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gtatctgaac taaggaccag aggtgccag atgtttctgg ctctcacgt gtccttcagg 420
acagaacaga agcacaaga ctcagccaag agttctcttt attcccttg atcctcccc 480
aagtgaggg cttaggcagc tgtagaacct caggaaagaa cggaatccag gcaatctgtt 540
tagagacccc ccaactccaaa tttatccttt tcctttcctt cccctaagat gtttccagg 600
ccctctggtg cccacactgt cctcttcctt ccacttgggg gtggggaaat ccttcctgcg 660
aggtcagggc atttctctac aaagtggcct gaatgaggcc aggccctgag aaggagccac 720
cagctggagg aaaggggctc caagccttgc tttaacacc cctgcaaaac cccaccctc 780
ccaagatgtt cacaaaaggt gagaaattca ggtacgaaac catcaatgga caacttgaaa 840
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<210> 284

<211> 1029

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (828)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (958)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (972)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (976)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (987)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1007)
<223> n equals a,t,g, or c

<400> 284
tgatggtgtg gtccaatgag cgggtcatgg gttgggtgtc cgggctgggc tgaaggaatt 60
tgccacgaac ctacaggaga gcggggtaca cggggcactg ctgcacctgg acgagacctt 120
cgactactcc gacctggcct tgetcctgca gatccccacg cagaatgcac aggcccgga 180
gcttctggag aaggaattca gcaaccttat ctcttaggc acagacaggc ggctggacga 240
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cctccgaggc gtaactcccc actcagctga gatgttgccc cccaactttc gttcggctgc 360
agcgggagcc ctgggctctc cggggctccc tctccgcaag ctgcagccag aaggccagac 420
ttctgggagt tcccgggcag acggcgtttc ggtccggacc tattcctgct agtgcaggcc 480
tccaggtgac ctcaactcga cggaagaatc ttcccaggc tgggctgttc cctctcctgc 540
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cacatgaact ggactgagag ggggaagaag cggggaggaa gaaatcccgc cccaaacgtc 720
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cctccctttt ttctgccc gtcgcggggc ccaagtcttt ccttcttcgt ccgaaaggag 900
gggaggggga ctctgtctac aagcctcgcc ccctgtgcca ctcagtccga cccgccngt 960
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ccgtgtttt 1029

<210> 285
<211> 1583
<212> DNA
<213> Homo sapiens

<220>

<221> misc feature
 <222> (1411)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1531)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (1557)
 <223> n equals a,t,g, or c

<400> 285
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 gccgagctga ccaacaggac acacagattc ctggagaaaag ccaaggcctt gaagatcagt 180
 ggtgtgatcg ggccttaccg tgagactgtg gactcggttg agaggaaagt cagcgagata 240
 aaagacatcc tggcgagag ccccgagca gagccactga aaaacattgg gaatctcttt 300
 gaggaagcag agaaactgat taaagatggt acagaaatga tggctcaagt agaagtga 360
 ttatctgaca caacttccca aagcaacagc acagccaaag aactggattc tctacagaca 420
 gaagccgaaa gcctagacaa cactgtgaaa gaacttgctg aacaactgga atttatcaaa 480
 aactcagata ttcgggggtgc cttggatagc attaccaagt atttcagat gtctcttgag 540
 gcagaggaga ggggtgaatgc ctccaccaca gaaccaaca gcaactgtga gcagtcagcc 600
 ctcatgagag acagagtaga agacgtgatg atggagcgag aatcccagtt caaggaaaaa 660
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 tcagccgstg ccgaaatgac ctgtggaaca cccccagggg cytcctgtty cgagaytgaa 780
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 gggggaggcc gaattttttg gaa 1583

<210> 286
 <211> 1177
 <212> DNA
 <213> Homo sapiens

<400> 286
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 aagayatctc aaaatgttta ccaatgtttt aagaagcttt gtgtgatatt cttccaaatg 120

```

tagttacca atataatat gtagaaaagg ctaaatacata cttaatgagc aaattgaagt 180
aagcttttaa agtatatttc tcttttggtg aaaggccaat ggagacattg tgaatttaag 240
tgaacatttg cctcaagatg ttaactataa acacactgca tacaattttc ttctgaataa 300
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aaataagtta tggcttaaaa tgcttttgga gtttatttct caaaattaaa atctgggtcac 420
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agtgacaatg caaggtaagt atatcaaagg aaatcaacag ttgtgcttg gggctttttg 540
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aaagtgaatg tttttctctt cagctgatct aaaaatgaaa gcaaratatc ttatgtagaa 720
atattttgat aatattttta cagtgaagct tcccattgtt ttatgtctta agtttctttg 780
ctgcgtttat gtaggttgca caagaacttt tactcacttg taattgtgcc tcagactttt 840
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agctaatagt agtttacaga caattctgat gattatgatt tcatttggtt taactaagct 1020
gtactagttc atttcataag gaaatgatac tgtagacaaa tgtaataaaa gcctgtgagt 1080
caagcatcaa gtggtgtttg ttagaaataa actagagatt tttaaaaaaa aaaaaaaaaa 1140
aaaaaaaaa aaaaaaaaaa acccccgggg gggggccc 1177

```

<210> 287

<211> 506

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (394)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (470)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (481)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (494)

<223> n equals a,t,g, or c

<400> 287

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acaagtagct gcagtacggg acggaattac agggtagacc caagcgtacg taaaatttaa 60
aaacaaagga ctatttataa atacagttta ttaacaaacg tgaactactt tctgttacat 120
taggtgttcc ctagtgtttc ttaatttctt tttagaaagt gtatttttat tagtattttt 180
ccggtgaaca gaagatttgt ttggatttaa acatttacta agacagtacc tattaggaaa 240
accaaataat gcaaattggtc aattcgattt taatttctca aaagatactc tggtatccag 300
aagattaaaa tgcctacatt gagtgcttaa aaaaaaaaaa acmactgtga tratktgagc 360

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223

```

agaatggcca gtaagttaag cttttttgga tccnggtaat ccagggtatc catttaccat 420
ggaaagggga ttccccaac tactggcca gagggagtt tggttttttn aaatttaagg 480
nggggaaatt ttanccctat aaaatt 506

```

```

<210> 288
<211> 948
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (3)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (926)
<223> n equals a,t,g, or c

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```

<400> 288
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gctgatgatt atcacccgga ggaaaatcga aggaagatgg gaaaaggcat accgctcaat 180
gaccaggacc ggattccatg gctctgtaac ttgcatgaca ttttactaag agatgtagcc 240
tcgggacagc gtgtggttct agcctgttca gccctgaaga aaacgtacag agacatatta 300
acacaaggaa aagatggtgt agctctgaag tgtgaggagt cgggaaagga agcaaagcag 360
gctgagatgc agctcctggt ggtccatctg agcgggtcgt ttgaggtcat ctctggacgc 420
ttactcaaaa gagagggaca ttttatgccc cctgaattat tgcagtgcca gtttgagact 480
ctggagcccc cagcagctcc agaaaacttt atccaaataa gtgtggacaa aaatgtttca 540
gagataattg ctacaattat ggaaacccta aaaatgaaat gacaatgatt ttgtatcagt 600
ggtccaaaca gaactaagca taaatcattg tgccatccca aacctcgttc cagccgcctt 660
gcccatacta gattctaaat gtttctaaa gcaaacccca atgtgtcaag acagacttgt 720
ttaggtgtaa ttttaggaat tatgtggtt catcaggaag cagaggggga gttttaaaag 780
tcaagcttaa attgaagttt aaattcatct ataaccaaat caaatgatca gaggaaattc 840
tgtaatcaat gctggaaatc gttacattgt ttagaacatt cttgctcatg cctgtatttg 900
cacaaataaa tgaaacttcg ctgtcnaaaa aaaaaaaaaa aaaaaaaaaa 948

```

```

<210> 289
<211> 1034
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (376)
<223> n equals a,t,g, or c

```

```

<400> 289
ggcacgagct cgtgccggtt tgacctggag catgggtcct ggaccaaatt gccccgcagc 60
ctgcgcagta gggataagag ggcagacttt gtggttgggt cccttggggg ccacattgtg 120
gccattgggg gccttggaag ccagccatgt cctttgggct ctgtggagag ctttagcctt 180

```

```
gcacggcggc gctgggaggc attgcctgcc atgcccactg cccgctgctc ctgctctagt 240
ctgcaggctg ggccccggct gtttggttatt gggggtgtgg cccagggccc cagtcaagcc 300
gtggaggcac tgtgtctgcg tgatggggtc tgaaggcttg gtgggagctg tccactggag 360
cagctcattg ccagangmrg ctatttctat ggctcctttt gctgctgagg aactcactg 420
tggctctgtg ggatgagaga ggcattgggg tgagcacttg aaacactgcc ttggggcctt 480
gggttagggg agcctttgtc tttagtgcag gacacacata tgcttacacc tacctttatc 540
accattcggt catgaatcat gcctagctcc atccttgccc tgggacctac taggccttcc 600
atccaactgg gaaatgggga gaagcaaagc tggcctcatg ctcttcaggg tcagttccta 660
tctggagttg accaggccta cccagttgc cattcctgaa aaatctcagc tgccaggctg 720
cctttagggt ccctgtagac ccaggagagt tgagagggtg ggggacacag agagaataga 780
gaggatgttg gaactgccag agggccggag cgcaggagtt caagtggagg aatgctggct 840
ttgagccctc tacactgctg gttgtatgac cttggacaag tcacttcacc tctctgtgcc 900
tcagcatcct catctataaa tggggatctc tgaacacctc ctaccctacc tacctcacag 960
ggctgttgtg aggaccagg gagtttggat gtggaagtaa aagtgtgtgt aaaacctaaa 1020
aaaaaaaaaa aaaa 1034
```

<210> 290

<211> 3091

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (24)

<223> n equals a,t,g, or c

<400> 290

```
cccagtagct cgtgccgctc gtgnccgcca actctcagtt tgatcttaaa gtctgaataa 60
taaaacaaat cccagcagta atacatttct taaacctcac agtgcagat atactttttc 120
attctgatcc tgtgtttgca aaaatataca catgtatatc atagttcctc actttttatt 180
catttgtttt cctattacct gtagtaaata tattagttag tacatggaat ttatagcatc 240
agctaccccc aggaacagca cctgacaggc gggggatttt ttttcaagtt gttctacatt 300
tgcataaatt atttctatta ttattcatgt atgttattta tttctgaatc acactagtcc 360
tgtgaaagta caactgcaag gcagaaagtg ttaggatttt gcatctaattg ttcattatca 420
tgggtattgat ggacctaaaga aaataaaaaat tagactaagc ccccaaataa gctgcatgca 480
tttgtaacay gattagtaga ttgaaatata tagatgtagt attttgggta tctagggtgtt 540
ttatcattat gtaaagggaat taaagtaaag gactttgtag ttgtttttat taaatatgca 600
tatagtagag tgcaaaaata tagcaaaaat aaaaactaaa ggtagaaaag cattttagat 660
atgccttaat ttagaaactg tgccagggtg ccctcggaat agatgccagg cagagaccag 720
tgccctgggtg gtgcctcctc ttgtctgccc tcatgaagaa gcttccctca cgtgatgtag 780
tgccctcgta ggtgtcatgt ggagtagtg gaacaggcag tactgttgag aggagagcag 840
tgtgagagtt tttctgtaga agcagaactg tcagcttggt ccttgaggct tccagaacgt 900
gtcagatgga gaagtccaag ttccatgct tcaggcaact tagctgtgta cagaagcaat 960
ccagtgtggt aataaaaaagc aaggattgcc tgtataattt attataaaat aaaagggatt 1020
ttaacaacca acaattccca acacctcaaa agcttggtgc attttttggg atttgagggt 1080
tttatctgaa ggttaaaggg caagtgtttg gtatagaaga gcagtatgtg ttaagaaaag 1140
aaaaatattg gttcgcgtag agtgcaaat agaactagaa agttttatag gattatcatt 1200
ttgagatgtg ttaaagtagg tttcactgt aaaaatgtatt agtgtttctg cattgccata 1260
gggcctgggt aaaaactttc cttaggtttc aggaagactg tcacatacag taagcttttt 1320
tccttctgac ttataataga aaatgttttg aaagtaaaaa aaaaaaaatc taatttggaa 1380
atttgacttg ttagtttctg tgtttgaaat catggttcta gaaatgtaga aattgtgtat 1440
```

```

atcagatact catctaggct gtgtgaacca gcccagatg accaacaatcc ccacacctct 1500
acatctctgt cccctgtatc tcttccttcc taccactaaa gtgttccttg ctaccatcct 1560
ggcttgtcca catgggtgctc tccatcttcc tccacatcat ggaccacagg tgtgcctgtc 1620
taggcctggc caccactccc aacttgacct agccacattc atctagagat ggttcctgat 1680
gctgggcaca gactgtgctc atggcaccca ttagaaatgc ctctagcatc tttgtatgca 1740
tcttgatttt taaaccaagt cattgtacag agcattcagt tttggctgtg gtaccaagag 1800
aaaaactaat caagaatata aaccacattc caggctgctg ttttctctcc atctacaggc 1860
cacactttta ctgtatttct tcataactga aattcattct gctattttca tatcagggta 1920
cagacttata aggggtgcatg ttccttaaag gtgcataatt attcttattc cgtttgctta 1980
tattgctaca gaatgctctg ttttgggtgt ttgagttctg cagacccaag aagcagtgtg 2040
gaaattcact gcctgggaca cagtcttata agaagtgttg cagggtgactt tgtatcagat 2100
gttgcttctc ttttctctgt acacagattg agagttacca cagtggcctg tcgggtccac 2160
cctgtgggtg cagcacagct ctctgaaagc aagaaccttc ctacctattc taacgttttt 2220
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caaaacttta agtaccctat cattaaaaat ctggttttaa aagtagctca agtaagggat 2580
gctttgtgac ccagggtttc tgaagtcaga tagccattct tacctgcccc ttactctgac 2640
ttattgggaa agggagaact gcagtggtgt ttctgttgca gtggcaaagg taacatgtca 2700
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agaatgaaaa ttaggtattt tattgtcaga tgatgaagtt cattgttttt ttcaaaattg 2820
gtgttgaaat atcactgtcc aatgtgttca cttatgtgaa agctaaattg aatgaggcaa 2880
aaagagcaaa tagtttgtat atttgaataa ctttttgtat ttcttacaat aaaaatattg 2940
gtagcaataa aaaataataa aaacaataac tttaaactgc tttctggaga tgaattactc 3000
tcctggctat tttctttttt actttaatgt aaaatgagta taactgtagt gagtaaaatt 3060
cattaaattc caagttttag caaaaaaaaaa a 3091

```

<210> 291

<211> 518

<212> DNA

<213> Homo sapiens

<400> 291

```

aggcatgaag aagagtgtgg gtactgtttc ctccacagcg gccagagtca ggggtggggag 60
tgagtccagt tgagggggaa acagtaccag cactgcgggg catgaagaag agtgtggggc 120
tgccggtggc cgtgcagtgt gtggctctgc cctggcaaga agagtttgtt ctgcggttca 180
tgccggagggt ggagcgactg atgaccctcg aaaagcagtc atcctgatgg ctctggctcc 240
agaggacctg agactcacac tctctgcagc ccagcctagt cagggcacag ctgccctgct 300
gccacagcaa ggaaatgtcc tgcatggggc agaggcttcc gtgtcctctc ccccaacccc 360
ctgcaagaag cgccgactcc ctgagtctgg acctccatcc ctgctctggt cccctctctt 420
cgctctgatc cctccacccc catgtggcag cccatgggta tgacatagcc aaggcccaac 480
taacagtcaa gaaacaaaaa aaaaaaaaaa aaaaattc 518

```

<210> 292

<211> 498

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature
 <222> (447)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (468)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (475)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (479)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (482)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (489)
 <223> n equals a,t,g, or c

<400> 292
 ctcgtgccg attcggcacg agcaacgtcg ctccagctgc tcttgacgac tccacagata 60
 ccccgaaagcc atggcaagca agggcttgca ggacctgaag caacaggtgg aggggaccgc 120
 ccagggaagcc gtgtcagcgg ccggagcggc agctcagcaa gtggtggacc aggccacaga 180
 ggcggggagcag aaagccatgg accagctggc caagaccacc caggaaacca tcgacaagac 240
 tgctaaccag gcctctgaca ccttctctgg gatcgggaaa aaattcggcc tctgaaatg 300
 acagcaggga gacttgggtc ggctctctga aatgayagca gggagacttg ggtgaccccc 360
 cttccaggcg ccatctagca cagcctggcc ctgatctccg ggcagccacc acctcctcgg 420
 tctgccccct cattaaaatt cacgttncca aaaaaaaaaa raaagggngg ccgcntagn 480
 gntccaagnt tagttacg 498

<210> 293
 <211> 469
 <212> DNA
 <213> Homo sapiens

<400> 293
 ggccagccct ggggcgcctt aaaaaccgga gctggcgctt ggcakcgcca ctctgggcag 60
 gatccaacgt cgctccagct gctcttgacg actccacaga taccggaag ccatggcaag 120
 caagggcttg caggacctga agcaacaggt ggaggggacc gccagggaag ccgccatgga 180
 ccagctggcc aagaccacc aggaaccat cgacaagact gctaaccagg cctctgacac 240
 cttctctggg atygggaaaa aattcgcct cctgaaatga cagcaggag acttgggtcg 300

227

```
gcctcctgaa atgayagcag ggagacttgg gtgaccccc ttccaggcgc catctagcac 360
agcctggccc tgatctccgg gcagccacca cctcctcggg ctgccccctc attaaaattc 420
acgttcccaa aaaaaaaaaa aaaaaaaaaa gggggggccc gtccccatt 469
```

<210> 294

<211> 668

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (568)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (650)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (652)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (658)

<223> n equals a,t,g, or c

<400> 294

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gcacagaagg gggaggccaa agtgggtggg agcgcgtgct gttgggagtt gcttgagggt 60
tgccggcgcg gggctgaagg ctagcaaacc gagcgatcat gtcgcacaaa caaatttact 120
attcggacaa atacgacgac gaggagttag agtatcgaca tgatcatgctg cccaaggaca 180
tagccaagct ggtccctaaa acccatctga tgtctgaatc tgaatggagg aatcttgggc 240
ttcagcagag tcagggatgg gtccattata tgatccatga accagaacct cacatcttgc 300
tgttccggcg ccactaccc aagaaaccaa agaaatgaag ctggcaagct acttttcagc 360
ctcaagcttt acacagctgt cttacttcc taacatcttt ctgataacat tattatgttg 420
ccttcttggt tctcactttg atatttaaaa gatgttcaat acactgtttg aatgtgctgg 480
taactgcttt gcttcttgag tagagccacc accaccatag ccagccaga tgagtgtctc 540
gtggaccaca gcctaagctg agtgtgancc cagaagccac gatgtgctct gtatccagac 600
acacttggca gatggaggaa gcatctgatt gagacatggt gtacaggtcn gnaatgcngt 660
ttgttttc 668
```

<210> 295

<211> 1400

<212> DNA

<213> Homo sapiens

<400> 295

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gctttgtcct ccagtggctg gtaggcagtg gctgggaggc agcggcccaa ttagtgtcgt 60
gcggcccgtg gcgaggcgag gtccggggag cgagcgagca agcaaggcgg gagggggggc 120
```

```

cggagctgcg gcggctggca caggaggagg agcccgggcg ggcgaggggc ggccggagag 180
cgccagggcc tgagctgccg gagcgggccc tgtgagttag tgcagaaagc aggcgcccgc 240
gcgctagccg tggcaggagc agcccgcacg ccgcgctctc tccctgggcg acctgcagtt 300
tgcaatatga ctttggagga attctcggct ggagagcaga agaccgaaag gatggataag 360
gtgggggatg ccctggagga agtgctcagc aaagccctga gtcagcgcac gatcactgtc 420
ggggtgtacg aagcggccaa gctgctcaac gtcgaccccg ataactgggt gttgtgcctg 480
ytggcgggcg acgaggacga cgacagagat gtggctctgc agatccactt caccctgac 540
caggcgtttt gctgcgagaa cgacatcaac atcctgcgcg tcacaacccg ggccggctgg 600
cggastcctg ctcttgagga ccgacgctgg ccccgcgggc agcgagggcg ccgagcagcc 660
cccgacctg cactgctgtt ggtgacgaat ccacattcat ctcaatggaa ggatcctgcc 720
ttaagtcaac ttatttgttt ttgccgggaa agtcgctaca tggatcaatg ggtccagtg 780
attaatctcc ctgaacggtg atggcatctg aatgaaaata actgaaccaa attgcaactga 840
agtttttgaa atacctttgt agttactcaa gcagttactc cctacactga tgcaaggatt 900
acagaaactg atgccaaggg gctgagttag ttcaactaca tgttctgggg gcccgagat 960
agatgacttt gcagatggaa agaggtgaaa atgaagaagg aagctgtgtt gaaacagaaa 1020
aataagtcaa aaggaacaaa aattacaaag aaccatgcag gaaggaaaac tatgtattaa 1080
tttagaatgg ttgagttaca ttaaaataaa ccaaatatgt taaagttaa gtgtgcagcc 1140
atagtttggg tatttttggg ttatatgccc tcaagtaaaa gaaaagccga aagggttaat 1200
catatttgaa aaccatatat tattgtatatt tgatgagata ttaaattctc aaagttttat 1260
tataaattct actaagtatt tttatgacat gaaaagtatt ttatgctata aattttttga 1320
aacacaatac ctacaataaa ctggtatgaa taattgcatc aaaaaaaaaa aagggggggc 1380
gctcgcgatc tagaaactag                                     1400

```

<210> 296

<211> 960

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (599)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (859)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (933)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (950)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (951)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (959)

<223> n equals a,t,g, or c

<400> 296

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gtcagcccgga gcccggtgcrg gccctttaag ggccggggggc gtgtagcggg cccgccccct 60
ccccgcgccg cccgcagtcg gttaagtgcg agccccggcg caggggcccg atctggcccg 120
gggcccggcg cgggtgtgga gcggcgcgtc atgtacacca tcaccaaggg gccagcaag 180
ctggtcgcgc agcgccgcac aggtcccacg cagcagcagg tggagggccg gctcggcgag 240
ctcctgaaat gccggcagcc cgcgcggccg acctcgcagc ccccgcgggc gcagccytth 300
gcgcascgcc gggacccttg cccctgtcga gtccagggcc aaggcttggt ttcaatcgtg 360
tgaatggccg gcgggccccc tccacgtccc catccttcga ggggaccag gagacctaca 420
cagtggccca cgaggagaat gtccgctttg tgtccgaagc ctggcagcag gtgcaacagc 480
agctggatgg tggcccagcc ggtgagggcg ggccaaggcc tgtgcagtag gtggagagga 540
cccccaatcc cgggtgcag aactttgtgc ccattgacct agacgagtgg tgggcgcanc 600
agttcctggc gagaatcacc agctgttcct agtggctgct gggagggggc gctgctacac 660
ggccgacctg tcgccaggag agaagcatgg cgccctgcc acccactgcg cctggctggg 720
tgccggccac acctgaagtg ccagcatttg gacttttgca ccttttttcc ccttggcccc 780
gtgtgtccaa ccaagctgcc atgccaaggg ccgaaccctg ctgacctcag cctgctcac 840
tgtgcccagg gaccagcgna caccctggg gctggcaggg aggagctcca ggctaataaa 900
gtggagaaac tgtcaaaaaa aaaaaaaaaa aanctcgagg gggggcccgn nccaattnc 960
```

<210> 297

<211> 657

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (29)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (86)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (88)

<223> n equals a,t,g, or c

<400> 297

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caaaagctgg agctccaccg cggtagcgn cgtctagaa ctagtggatc cccggggctg 60
caggaattcg gcacgagctc gtgccngncc tttggagcag agaggaggca atggccacca 120
tggaagaaca ggtgatctgc gccctgggtc tgggtgtccat gctggccctc ggaccctgg 180
ccgaggccca gacagagacg tgtacagtgg ccccccgtga aagacagaat tgtggttttc 240
ctggtgtcac gccctcccag tgtgcaaata agggctgctg ttctgacgac accgttcgtg 300
```

```

gggtcccctg gtgcttctat cctaatacca tcgacgtccc tccagaagag gagtgtgaat 360
tttagacact tctgcaggga tctgcctgca tcctgacgcg gtgccgtccc cagcacgggtg 420
attagtccca gagctcggct gccacctcca ccggacacct cagacacgct tctgcagctg 480
tgctcggct cacaacacag attgactgct ctgactttga ctactcaaaa ttggcctaaa 540
aattaaaaga gatcgatatt aaaaaaaaaa gaaaaggaaa aaaaaggcg gccgtctaag 600
aggatccaag cttacgtaac gcgtgcatgc gaaggcata gctcttctat agtgtca 657

```

<210> 298

<211> 892

<212> DNA

<213> Homo sapiens

<400> 298

```

gcagccaggc tctcaggga ggtccatgct gcttggcctg agttcaaggc tttctgcctg 60
tagcctggac tcccgtggac cccgtgggc aggtggcttc cccgtggcat ctccacaccg 120
cctctgcctg cccctgtgga ctgatgctat cgcgcaccgt cccacgacct caccctgagc 180
tcctgaagcc ggggtctgag cctgcatcac ctctggcctc tcatccccc ctctcctgag 240
agcagtggtc acagcgccg gccgctctgc tgagaaggca gagaggcagg ctccaggcctc 300
agcgtggaca gcagggataa ggggcacgaa ggacggggac tcggcccctt cagaattcct 360
caggactctc aggtgcagct ttgccaaaaa ggaacttttc atgtcatgca gttgagggga 420
cttagtctca atcccaggct cctcttgact ctgggcagct ttaatcaggc tgggcagcct 480
ctgctacagc gtggagtgg atggctctct tccctcagcc acgccgcttg tgaggacaga 540
ggtgggggag tgggaagtgg gaagtcacca gagaacagga gagggatttg agggcgcgac 600
cccagcgctc tccacggacc agccagaggg actggagcca ggtgtgcatg ggttcaggc 660
cctggccctg cccagcctct gtcttgggag ctcagcccca gggttcgggc gtcagcagtt 720
tcccaagaac aagatgtgat ggcatctgct gctgaaaccc tgataggac caggccccct 780
gcaccgctgt cagcctgagg aattaaagct ttggtgctgg gaaragcaaa aaaaaaaaaa 840
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa tc 892

```

<210> 299

<211> 1624

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1621)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1623)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1624)

<223> n equals a,t,g, or c

<400> 299

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ccggggctgc aggaattcgg cagagagag gaggtccac aggtcctgc cctgggctac 60

```

```

cgagtcccc gatggtgtta tacattaaat atccaggatg gagaagccac atgctactca 120
ccgaaggagg aaattatcac agcagcctgg gcacgcgttg tgagctctcc tgtgaccggg 180
gctttcgatt gattggaagg aggtcgggtg aatgcctgcc aagccgtcgt tggctcggaa 240
ctgcctactg caggcagatg agatgccacg cactaccatt catcactagt ggcacttaca 300
cctgcacaaa tggagtgtt cttgactctc gctgtgacta cagctgttcc agtggctacc 360
acctggaagg tgatcgagc cgaatctgca tggaaagtgg gagatggagt ggaggcgagc 420
ctgtatgtgt agacatagat cccccaaga tccgctgtcc ccactcacgt gagaagatgg 480
cagagccaga gaaattgact gctcgagtat actgggaccc accgttgggt aaagattctg 540
ctgatggtac catcaccagg gtgacacttc ggggccctga gcctggctct cactttcccg 600
aaggagagca tgtgattcgt tacactgcct atgaccgagc ctacaaccgg gccagctgca 660
agttcattgt gaaagtacaa gtgagacgct gcccaactct gaaacctccg cagcacggct 720
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gcggttatga tcgccagggg acaccctccc ggtctgtca gtccagccgc cagtggtcag 840
gttcaccacc aatctgtgct cctatgaaga ttaacgtcaa cgtcaactca gctgctggtc 900
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<210> 300

<211> 1969

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (13)

<223> n equals a,t,g, or c

<400> 300

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<210> 301

<211> 1882

<212> DNA

<213> Homo sapiens

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<222> (223)

<223> n equals a,t,g, or c

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<221> misc feature

<222> (1840)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1849)

<223> n equals a,t,g, or c

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<210> 302

<211> 2804

<212> DNA

<213> Homo sapiens

<400> 302

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<210> 303

<211> 3859

<212> DNA

<213> Homo sapiens

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<221> misc feature

<222> (581)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (889)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (890)

<223> n equals a,t,g, or c

<400> 303

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<211> 3378

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

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<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1350)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3361)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3365)

<223> n equals a,t,g, or c

<400> 304

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<213> Homo sapiens

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<221> misc feature

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<223> n equals a,t,g, or c

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<222> (2166)
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<221> misc feature
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241

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<213> Homo sapiens

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<222> (6158)

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<400> 309

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<210> 310

<211> 2086

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1763)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1769)

<223> n equals a,t,g, or c

<400> 310

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cgctcccca cgcgctcaga gatcctcagc aacgcgggtc tcaggtttga ggtggtcccc 180
tccaagttaa aagagaagct ggacaaagcc tccttcgcta ctccgtatgg gtacgccatg 240
gagaccgcca agcagaaggc cctggagggt gcccaaccggc tgtaccagaa agacctgcgg 300

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gccccgcagc tggtcattgg agcggacacg atcgtgacag tcggggggct gattctggag 360
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agcgtgttca cagggtgtcg cgtcgtccac tgctccagca aagaccatca gctggacacc 480
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aagaaagcaa aagccaaaaa aaaaaaaaaa aaaaatttgg gggggg 2086

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<210> 311

<211> 2163

<212> DNA

<213> Homo sapiens

<400> 311

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aaa 2163

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<210> 312

<211> 1397

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1397)

<223> n equals a,t,g, or c

<400> 312

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accagcccag cccaggatg tgtcgacca gcagctctgc ctgggtggcc tgcagtgccg 1080
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aaaaaaaaa aaaaaan                                     1397
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<210> 313

<211> 4106

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (344)

<223> n equals a,t,g, or c

<400> 313

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tgaaaggagt ttgctgagtg ggagtatttg caaaaggatt acttctccga ggagatagaa 1860
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<210> 314

<211> 532

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (497)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (498)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (502)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (524)

<223> n equals a,t,g, or c

<400> 314

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<210> 315

<211> 1938

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1270)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1455)

<223> n equals a,t,g, or c

<400> 315

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<210> 316

<211> 818

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (55)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (814)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (818)

<223> n equals a,t,g, or c

<400> 316

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250

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<210> 317

<211> 837

<212> DNA

<213> Homo sapiens

<400> 317

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cgtgtgcgtg gacctgggtg actgggaggc caccgagcgg gcgctgggca gcgtggggcc 240
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ggtggaaggg ggcttctggg cctgctgagc tccctccaca cacctcaagc cccatgccgt 780
gctcatccta ccccaatcc ctccaataaa cctgattctg ctgccccaaa aaaacga 837

<210> 318

<211> 1448

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (878)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1198)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1395)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1397)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1445)

<223> n equals a,t,g, or c

<400> 318

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ctgcaggcag gttgttgggt ttcgaggcca acggggccaa cgggtctaaa gcaggtaggg 180
gcggctgtga agtgaggggg tctaggggag aaaaggggac ggagagcaga ggaaggggtg 240
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aaacntgg                                     1448

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<210> 319

<211> 1493

<212> DNA

<213> Homo sapiens

<400> 319

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aaaatactcc aaccttttct tggaaagtca taacatctca ctgactgaac attccagtgt 180
gccagtggaa aaaaatatca ctttagaacg accttctgct gtagaactca catgtcagtt 240
cacaacttct ggggatgtga attcagtaaa tgtgacttgg aaaaaagggg atgaacaact 300
taagaattac catgtcagtg ccacagaagg catcctgtat acccagtaca agttttccat 360
cattaatagc gaacaactgg gaagctattc ttgtttcttt gaagaggaaa aggaacgaag 420
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tgtgggggat tccgttgtct tgggtgtgaa atgccgacac tgtgctcctt taaattggac 540
ctggtacagt ggtaatagga gtgtacaggt tcctcttgat gttcacatga atgaaaagta 600

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tgcgatcaat ggaacaaacg cgaatgaaac aaggcttaag ataatgcagc tttcagaaga 660
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tgaactgggt gtgataagtt atttgggtgcc cctcaaacca tttcttgga tagttgttga 780
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<210> 320

<211> 609

<212> DNA

<213> Homo sapiens

<400> 320

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gagcatccag cgagtcctgc aggctgtgga taaagccaat ggatactgtt tcggagccca 180
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<210> 321

<211> 502

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (458)

<223> n equals a,t,g, or c

<400> 321

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tgcccgggcc ccactaggc ccagtgtctg gtcagagagg cgtttccatc aaccagtttt 240
gcaaaggatt caatgagagg acaaaggaca tcaaggaagg cattcctctg cctaccaaga 300
ttttagtgaa gcctgacagg acatttgaaa ttaagattgg acagcccact gtttcctact 360

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tcctgaaggc agcagctggg attgaaaagg gggccccggca aacagggaaa gaggtggcag 420
gcctggtgac cttgaagcat gtgtatgaga ttgcccgnat caaagctcag gatgaggcat 480
ttgcctgcag gatgtacccc tg 502

<210> 322

<211> 2630

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1952)

<223> n equals a,t,g, or c

<400> 322

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acccttcagg caccctctga cagcccagga tgctgttgga caccctctc ctctccctcc 180
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<210> 323

<211> 1874

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (67)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1735)

<223> n equals a,t,g, or c

<400> 323

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cacctcagcc ctaa 1874

<210> 324

<211> 2325

<212> DNA

<213> Homo sapiens

<400> 324

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cttgtctgtg gtgctgtttt tttccctact gcagtggact tatgctgttt tcatgtttag 2040
aaacaaaaag gtttcatgtg attcatgtgt aagatgcaca gtatttgaca tcctgattat 2100
gtaatcccta ttccatctat ccagtcttac acttatggtt ggcctcaaat ctattgcatt 2160
tatgataatg tattatatct agttgagttt aatatttttt tattagcctg taaataaaga 2220
tggcatcttc tacattaaaa tgatattgat ctcatttttt taaataaaca ttttgtttcc 2280

ttgacgttaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa 2325

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<211> 785

<212> DNA

<213> Homo sapiens

<220>

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<222> (6)

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<400> 325

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ggagagcccc gagctgctga accctgagcc caggagactg agcccagagt tgaggctact 180
gccctatatg atcactctgg gcgacgccgt gcacaacttc gccgacgggc tggccgtggg 240
cgccgccttc gcgtcctcct ggaagaccgg gctggccacc tcgctggccg tgttctgcca 300
cgagttgcca cagcagctgg gggacttcgc cgcttgctg cagcgggggc tgtccgtgcg 360
ccaagcactg ctgctgaacc tggcctccgc gtcacggcc ttcgctggtc tctacgtggc 420
actcgcggtt ggagtcagcg aggagagcga ggctggatc ctggcagtgg ccaccggcct 480
gttcctctac gtagcactct gcgacatgct ccggcgatg ttgaaagtac gggaccgcgc 540
gccctggctc ctcttcctgc tgcacaacgt gggcctgctg ggcggctgga ccgtcctgct 600
gctgctgtcc ctgtacgagg atgacatcac cttctgatac cctgccctag tccccacct 660
ttgacttaag atcccacacc tcacaaacct acagcccaga aaccagaagc ccctatagag 720
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aaaaa 785
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gacgacagaa gggtagcggt gcgagaagac kacagaaggg tacggctgcg agaagackac 180
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<210> 327

<211> 2454

<212> DNA

<213> Homo sapiens

<400> 327

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tcccaccctc ccgccccgcg gcagccctag ctccctccac ttggctcccc tgggtcccgt 180
cgctcggccg ggaagctgctc tgtgcttttc tctctgattc tccagcgaca ggacccggcg 240
ccggcactga gcaccgccac catggggaag ggggttggac gtgataagta tgagcctgca 300
gctgtttcag aacaaggtga taaaaagggc aaaaagggca aaaaagacag ggacatggat 360
gaactgaaga aagaagtttc tatggatgat cataaactta gccttgatga acttcatcgt 420
aaatatggaa cagacttgag ccggggatta acatctgctc gtgcagctga gatcctggcg 480
cgagatggtc ccaacgccct cactccccct cccactactc ctgaatggat caagttttgt 540
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gcttatagca tccaagctgc tacagaagag gaacctcaaa acgataatct gtacctgggt 660
gtggtgctat cagccgttgt aatcataact ggttgcttct cctactatca agaagctaaa 720
agttcaaga tcatggaatc cttcaaaaac atggtccctc agcaagccct tgtgattcga 780
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gagtacacct ggcttgaggc tgctatcttc ctcatcggtt tcatcgtagc caatgtgccg 1260
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<210> 328

<211> 505

<212> DNA

<213> Homo sapiens

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aaagagaaac tttttcccag ctgggtgctg tggctcacac ctgtgaatcc cagccctttg 180
gnaggctgna gtgggcagat cgcttgagcc caggagtgtg agatcagcct gggcaacatg 240
gtgaantcca tctctgtgaa aaatacaaaa attagccagg tgtggtggtg cgcgcctgtn 300
antcccagct actagggagg ctgaagggtg gnggnttgnt tnagcccagg aggttgaggc 360
tgcattnggc tgggattcaa accatgttac tccntgacca ngtgngncct ntttcaaann 420
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<210> 329

<211> 559

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<222> (553)

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<400> 329

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ttagttgcac tagccatatt tcaaatactt gatggataca tgtggctagt ggctaacata 180
agggatagca cagatataaa acatttcctc ccaaagtgtt gggattacag gcatgagcca 240
ccgcgcccgg cctatcatat gaattttgag ggaacacaat catgcagtct gtagcagatg 300
gtaataggct gatataattac acttgttgat gtaanctgga tangtttctt tcttctccaa 360
ggacagcttt ttnaatattht aacantncca ttaatttttc agtttccggg agaattttat 420
aatttataaat tgccgactta ngganaancc aattggncca accattacaa tanattttta 480
attccgntta aaaaatccca ccngnggggg aattccgctt aaaattttat tttccattat 540
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<211> 467

<212> DNA

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<400> 330
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ctggncagac accgntgnaa cggnattat ttcaccctca gagagaggct gatcactatg 180
caaaaacaac tgggaggaaa cccagaagta tattgaatga gcagtgcaga ttagagttgc 240

267

ccatatcgat gggcancaat tgncaattat tgtgnagcaa tacacacggg gtttccangg 300
gagtnntaaa tgccttaaag taattaaaaan ccgggggcaat nccntttttac ggatgttttg 360
ctgggggtttc cgtttttaac caacattttt ntnggggncc gnccacaaat tttgggggttg 420
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<211> 418

<212> DNA

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<220>
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<400> 331
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aatgtngcca ntgtctgtct gcagattggc tacccaactg ttgcatcagt accccattct 180
atcatcaacg ggtacnaacg antcctggcc ttgtctgtgg agacggatta caccttcca 240
cttgctgaan aagtcanggc ttcttggtg atccatctgc cttingtggt gctgcccngt 300
tggtgctgc caccacaact gtcctgctg ctgctgcnc ccancctaag ttnaaaccca 360
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<210> 332
<211> 486
<212> DNA
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<220>

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<222> (49)

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tcacggccac cgtcatcctt gtctcgcccg gggaaacctt cctgggtgtac acagaccggc 240
tctattctcg ctcggaactt aacaactacg tggtctgtgt atacaagggtg ctggggactt 300
cctgtttggg gctgccgtga gccagtctct gacagacctg gccaaagtaca tgattgggcg 360
tctgaagccc aattctaanc gtctgcgaac ccgattgaac cggatcaatgc tcgtnatgtg 420
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486

<210> 333

<211> 268

<212> DNA

<213> Homo sapiens

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catcaaagtc tactacacct tgagaaaaca aatgaacgan aatctatttt cctcattcat 180
taccccaaca ataataggac tccctatcgt aattattntc actatgtttc caagcattga 240
tatncccatc acctacccgn ctntcaa 268

<210> 334
<211> 517
<212> DNA
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<222> (436)

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<220>

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<222> (463)

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<220>

<221> misc feature

<222> (489)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (496)

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<400> 334

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taactggcta gaagtgccca acgtggaatg tttctttttt aaaggcggct cttgaagcga 120
cccgggaagcg gaagtgggaag aaagtctctag tggcttgaga ttaagcctga tcaagatgac 180
aacctcccaa aagcaccgag acttcgtggc agancccatg ggggagaacc agtgggggaaac 240
ctggctggga ttggtgaant cctgggcaag aaactggaag aaagggtttt gacaaggcta 300
tnttgtcttg gccatttctg gtgctaaaaa anataaaaaac tctcccggaa tggtgaaaaan 360
ctttttgggc caccacaacat cccgaatgtc cgatgctcca aaatgtgcan cctcttttat 420
gtctttggaa tctctncccc ccccccattt tgaccaattg ganccccctt cctcaagaaa 480
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<211> 297

<212> DNA

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<220>

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<220>

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<222> (245)

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<220>
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<400> 335
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ggccgctcta gaactagtg ggggcccggt acccaattcg ccctatagtg agtcgtatta 120
caattcactg gccgtcggtt tacaacgtcg tgacnnggaa aacntnnaat ncttccggct 180
cgtatgttgt gtggaattgt nagecgataa caattcacac aggnancagc tataaccatg 240
attnnnccaa gntcgaaatt aacntnact aaaggggaca aaagtngggg ctccacg 297

<210> 336
<211> 386
<212> DNA
<213> Homo sapiens

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<220>
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<220>

<221> misc feature

<222> (251)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (261)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (265)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (272)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (275)

<223> n equals a,t,g, or c

<220>
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<222> (286)
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<220>
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<222> (304)
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<220>
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<222> (322)
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<220>
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<222> (328)
<223> n equals a,t,g, or c

<220>
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<222> (337)
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<220>
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<222> (365)
<223> n equals a,t,g, or c

<220>
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<222> (380)
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caaaatgctg ctgggtgttt atgcctactt tatagagcat aagcagcgca acacccttat 120
ctggttgncg acggatggtg atgcccngga actttatgaa aaaccacgt tgagcccgac 180
tattngngat attccgtcgn tgcntggggc tggcccgtg gtatggcaaa aaagcaccgg 240
gttnaacaag ntcaaccatg naagngttcc anctnaatgg gggggncccc gtaaccaaat 300
tngncctata agtnnatggg antttaanaa ttcaatnggc cctngntttt aaatggtgng 360
tgntnggcct tttttttttn gtttgt 386

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<220>
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<220>
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<222> (412)
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<220>
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<222> (414)
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<220>
<221> misc feature
<222> (437)
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<220>
<221> misc feature
<222> (439)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (469)
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<220>
<221> misc feature
<222> (470)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (471)
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<220>
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<222> (472)
<223> n equals a,t,g, or c

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<220>

<221> misc feature

<222> (483)

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<222> (501)

<223> n equals a,t,g, or c

<400> 337

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caccactatg taccctggca ttgccgaccg aatgcagaag gagatcacgg ccctagcacc 120
cagcaccatg aagatcaaga tcattgcccc tccggaggcg caaatactct gtctggatcg 180
gtggctccat cctggcctct ctgtccacct tccagcagat gtggatcagc aaacagggaa 240
tacggtgaag ccgggccttc cattgtccac cgcaaagtct ttcttaaaac acttttcctg 300
gttcctnttc tgtcttttag gcacacaact gtggaatgtn cctgtgggaa tttatggccn 360
tttcagtttc tttttccaaa tcattcctag ggccaaagtt ttgnattggt tnanccatgg 420
ggttttttta aataaantnt ggaaataggg ttaattgggt aaaaaaaann nnaaaaaaaa 480
ntntgggggg ggggggcccg ntaccc 506
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<210> 338

<211> 623

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (441)

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<220>

<221> misc feature

<222> (508)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (509)

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<220>

<221> misc feature

<222> (513)

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<222> (537)

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<222> (565)

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<220>

<221> misc feature

<222> (597)

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<220>

<221> misc feature

<222> (599)

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<220>

<221> misc feature

<222> (612)

<223> n equals a,t,g, or c

<400> 338

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aagaaggagc tgtctgacat cgctcaccgc atcgtggcac ctggcaaggc catcctggct 120
gcagatgagt ccaactgggag cattgccaaag cggctgcagt ccattggcac cgagaacacc 180
gaggagaacc ggcgcttcta ccgccagctg ctgctgacag ctgacgaccg cgtgaacccc 240
tgcattgggg gtgtcatcct ctccatgag acaactctacc agaaggcgga tgatgggcgt 300
cccttccccc aagttatcaa atccaagggc ggtgttgtgg gcatcaaggc agacaagggc 360
gtggtccccc tggcagggac aaatggcgag actaccaccc aagggttgga tgggctgtct 420
gagcgctgtg cccagtacaa ngaaggacgg agctgacttc ggccaagtgg cgttgtgtgc 480
ttaagaatgg gggaacacac cccctcannc ctnggcata tggaatatgc caattgntct 540
ggccccgtat gccagtatct ggcancagaa tgcattgggc cattcgggga gtctgananc 600
tcctgatggg ancatgactt gaa 623
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<210> 339

<211> 344

<212> DNA

<213> Homo sapiens

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<220>

<221> misc feature

<222> (157)

<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (171)
<223> n equals a,t,g, or c

<220>
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<222> (210)
<223> n equals a,t,g, or c

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<221> misc feature
<222> (298)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (330)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (343)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (344)
<223> n equals a,t,g, or c

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ttttttatat ttcaactaaa agtatcanaa tatagctttc cagaaaaccc cgaaccaaag 120
tcactgacta catcaaagtc tactacacct tggaganaac aaatgaacga naatctattt 180
tcctcattca ttacccaac aataataggn ctocctatcg taattattat cactatgttt 240
ccaagcatta tattcccatc acctaccga ctaatcaata atcgactcat ctccattnca 300
acaatggatt agtgcantga acatgcaaan gcaaggatta tcnn 344

<210> 340
<211> 345
<212> DNA
<213> Homo sapiens

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<220>
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<222> (13)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (31)
<223> n equals a,t,g, or c

<220>
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<222> (88)
<223> n equals a,t,g, or c

<220>
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<222> (90)
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<220>
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<222> (128)
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<220>
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<222> (135)
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<220>
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<220>
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<222> (153)
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<220>
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<220>
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<220>
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 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (313)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (339)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (343)
 <223> n equals a,t,g, or c

<220>
 <221> misc feature
 <222> (345)
 <223> n equals a,t,g, or c

<400> 340
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 ggaattcccg ggtcgaccca cgcgtccngn aggaggggac agctgcgggc gcggggaggg 120
 ggcgcgngc cgcgngngc catggnggac agnagagccg ggagtcagag annccggccc 180
 gcagcccag atgtcgccgc catggcttcg ccgcagctct gccgcgcgct ggtgtcggcg 240
 caatgggtgg cggaagcgt gcgggccccg cgcgctgggg cagcctctgc agctgntagg 300
 acgcctcctg gtnacctggc cggaagctgg ggggcgcgna cgncn 345

<210> 341
 <211> 170
 <212> DNA
 <213> Homo sapiens

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<220>
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<220>

<221> misc feature

<222> (43)

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<222> (160)

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<222> (163)

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<222> (164)

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<220>

<221> misc feature

<222> (170)

<223> n equals a,t,g, or c

<400> 341

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tccaagctta cttggacatg catgcnacgt catagctctt ctatagtgtc acctaaattc 120
aattcactgg ccgtcgtttt acaacgtcgt gactgggaan atnntaaaaan 170
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<210> 342

<211> 387

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (238)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (273)

<223> n equals a,t,g, or c

<220>
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<222> (328)
<223> n equals a,t,g, or c

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<220>
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<220>
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<222> (366)
<223> n equals a,t,g, or c

<220>
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<222> (384)
<223> n equals a,t,g, or c

<400> 342
aatgacttgg ttgagtactc accagtcaca gaaaagcattc ttacggatgg catgacagta 60
agagaattat gcagtgtctgc cataaccatg agtgataaca ctgcggccaa cttacttctg 120
acaacgatcg gaggaccgaa ggagctaacc gcttttttgc acaacatggg ggatcatgta 180
actgccttgg atcgttggga accggagctg aatgaagcca taccaaacga cgagcgtnac 240
accacgatgc ctgtagcaat ggcaacaacg ttngcaaact attaactggc ggactactta 300
ctctagcttc ccggcaacaa tttatagnct tggtggnnggc gggtaaagtt ncaaggccca 360
tttttngggt tggccttcgc gttngtt 387

<210> 343
<211> 186
<212> DNA
<213> Homo sapiens

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<220>
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<221> misc feature
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<220>
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<222> (109)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (152)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (153)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (160)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (183)
<223> n equals a,t,g, or c

<400> 343
gctgcaggaa attaacagag tctacnagga aatgtacaag actgatctgg agaaagacat 60
tatntcggac ncatctggtg acttccgcaa gctgatgggt gccctggcna aagggttaaaa 120
aacagaagaa tgggtccgtcc ttgaatatga anngaatan ccacatgccc ggatttcctt 180
gancccc 186

<210> 344
<211> 611
<212> DNA
<213> Homo sapiens

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<220>
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<222> (11)
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<220>

<221> misc feature

<222> (285)

<223> n equals a,t,g, or c

<400> 344

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cgctctagaa ctagtggatc ccccgggctg caggaattcg gcacgagctg cgttgggctc 120
cggaagccg ttcgggctgg ggctgtcggc cgcggggcgg aggcactcgc gcgggggatg 180
gcccactgcg tgaccttggt tcagctgtcc atttctgtg accatctcat tgacaaggac 240
atcggtcca agtctgacct actctgcgtc cttttacagg atgtnggagg gggcagctgg 300
gctgagcttg gccggactga acgggtgcgg aactgctcaa gccctgagtt ctccaagact 360
ctacagcttg agtaccgctt tgagacagtc cagaagctac gctttggaat ctatgacata 420
gacaacaaga cgccagagct gagggatgat gacttcctag ggggtgctga gtgtcccta 480
ggacagattg tgtccagcca ggtactgact ctccccttga tgctgaagct ggaaaacctg 540
ctgggcgggg gaccatcacg gtctcagctc aggaattaaa ggacaatcgt gtagtaacca 600
tgaggtaga g 611
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<210> 345

<211> 344

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (289)

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<220>

<221> misc feature

<222> (296)

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<220>

<221> misc feature

<222> (329)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (331)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (342)

<223> n equals a,t,g, or c

<400> 345

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tttcttcta cagtattcct gaatttgacg aatggaaaaa acatatagaa aaccagaaaag 60
cctggaaaat aaagtactat aaaggattgg gtactagtac agctaaagaa gcaaagggaat 120
atthtgcgtg tatggaaagg catcgcatct tgtttagata tgctgggtcct gaagatgatg 180
```

```

ctgccattac cttggcattt agtaagaaga agattgatga cagaaaagaa tggttaacaa 240
atatttatgga agaccggaga cagcgtagct acatggctta ccagaggant gattcnctct 300
caactcagac atgaaagatc tataccacnc ntgttgatgg cntt 344

```

```

<210> 346
<211> 506
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (392)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (452)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (453)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (472)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (480)
<223> n equals a,t,g, or c

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```

<220>
<221> misc feature
<222> (495)
<223> n equals a,t,g, or c

```

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<400> 346
ggaaaagccc aaggaaaaag caaagaatag caaaaaaaag ggggccaaga aggaagtggg 60
tgggattggg cttctttttt cttcagttag ttttttcccc aacagggttct gatggtcctt 120
tggctaccag caaaccagtc cctgcagaaa agtcagggtct tccagtgggt cctgagaacg 180
gagtagaact ttccaaagag gagctgatcc gcaggaagcg cgaggagtcc attcagaagc 240
atgggagggg tatggagaag tccaacaagt ccacgaagtc agatgctcca aaggagaagg 300
gcaaaaaagc accccgggtg tgggaactgg gtggctgtgc taacaaagaa atgttgatt 360
acagtacttc caccaccaat ggaaccctg angcttgctt tgtctgagga cattaacctt 420
gattccaagg gactgggtct ggggggcact tnnngatctg gactgcacac tntgatgacn 480
aagggttgtg taaantttcc aaacta 506

```

```

<210> 347

```

289

<211> 444
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (289)
<223> n equals a,t,g, or c

<400> 347
cggaagggag accatgttcc gagcggcggc tccggggcag ctccggcggg cggcctcatt 60
gctacgattt cagagtaccc tggtaatagc tgagcatgca aatgattccc tagcacccat 120
tacttttaaat accattactg cagccacacg ccttggaggt gaagtgtcct gcttagtagc 180
tggaacaaaa tgtgacaagg tggcacaaga tctctgtaaa gtagcaggca tagcaaaaagt 240
tctggtggct cagcatgatg tgtacaaagg cctacttcca gaggaactna caccattgat 300
tttggcaact cagaagcagt tcaattacac acacatctgt gctggagcat ctgccttcgg 360
aaagaacctt ttgccagag tagcagccaa acttgagggt gccccgattt ctgacatcat 420
tgcaatcaag tcacctgaca catt 444

<210> 348
<211> 358
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (52)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (187)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (280)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (295)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (301)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (348)
<223> n equals a,t,g, or c

<400> 348
ggcagagaag cagaagcgnc tcagttagag tccagcaaaa ggtttgccaa anagtttatg 60
gacagacatg gaatcccaac cgcacaatgg gaaggctttc accaaacctg aaaggaagcc 120
tgcagcttca ttttgagtgc agacttcctt gctttggttg tgaaaggcca gtggtcttgc 180
agctggnaaa aggggtgatt gttgcaaaga gcaaagaaga ggcttgcaag ctgtacaaga 240
gatcatgcag gtaggctggg tcttctggaa aaatttactn ttgtattcat actgnatgaa 300
ntaccgtttt aagtttnaaa aatgttcctc acattaaggg aaattctntt ttgcaacc 358

<210> 349
<211> 321
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (187)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (206)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (240)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (294)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (295)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (301)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (316)
<223> n equals a,t,g, or c

<400> 349
ggcgctttgc tctgtccacc aagattcctg acaccaaagg ctgcttgacg tgtcgtgtgg 60
tgcggaaccc ctacacgggt gccaccttcc tgctggccgc cctgcccacc agcctgctcc 120
tgctgcagtg gtatgagccg ctgcagaagt ttctgctgct gaagaacttc tccagccctc 180
tgcccanccc agctgggatg ctgganccgc tgggtgctgga tgggaaggag ctgccgcagn 240
gtttttttgg ggccgaaggg cctaaagggc ccggttgccg gttcctgttc caanncctgc 300
ncctgggagg ttggcnttaa g 321

<210> 350
<211> 742
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (618)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (653)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (658)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (683)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (689)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (702)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (707)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (714)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (719)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (722)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (734)

<223> n equals a,t,g, or c

<400> 350

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ggtcacgctg acccagtgtc cggaagagct ggtgcagctc atcctgcacg aatacaagat 60
cttcaatgca gaagtgtctt tccgagaaga ctgctccccg gacgagttca tcgatgtgat 120
cgtgggcaac cgggtgtaca tgccctgcct gtatgtttat aacaaaatcg accagatctc 180
catggaagag gtggaccgcc tggcccgaaa acccaacagt gtggtcatca gctgcggcat 240
gaagctgaac ctggactatc tgctggagat gctctgggag tacttggccc tgacctgcat 300
ctacaccaag aagagaggac agaggccaga cttcacagac gccatcattc tccggaagg 360
ggcctcagtg gagcacgtgg gcaccagcac caagtacagt ccgcagcggg tgggcctgac 420
ccacaccatg gagcatgagg acgtcatcca gatcgtgaag aagtaacggc gcctgccggg 480
ccttccgccc acctgctcgt ctcccttggg aggtggtccc actgggacac acaaacaccc 540
aaacagaaaa atacaaatac acgtacccca agaaggggtc cctcaagtct ctgctattta 600
cagaagtttc ttcagtangc agacaaaaa tgtgttgggc aaaagggctc ggntggangc 660
atthccata agactgagcc ctnttcatng ggggttttga gnttgantgc ttancctgna 720
tntgtgcctc caanccctg ac 742
```

<210> 351

<211> 272

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (167)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (251)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (272)

<223> n equals a,t,g, or c

<400> 351

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aatcaggcgg gactgacggc agatcgatg ctggctcctgt ccagagccgg gcaggcggca 60
gggctgacgt ttaaccagac cagcgagtca ctcagcgcac tggttaaggc gggggtaagc 120
ggtgaggctc agattgcgtc catcagccag agtgtggcgc gttctctnctc tgcacccggc 180
gtggagggtg acaaggctcg tgaagccttc gagggggggc cgtacccatt tgcctatagt 240
aagcgtatta naataattgc cgtgttttaa an 272
```

<210> 352

<211> 256

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (170)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (236)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (248)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (251)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (252)

<223> n equals a,t,g, or c

<400> 352

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gcagacgtcc agagcagagt cagccagcat gaccgagcgc cgcgtcccct tctcgctcct 60
gcggggcccc agctgggacc ccttcgcgca ctggtaccgc catagccgcc tcttcgacca 120
```

```
ggccttcggg ctgccccggc tgccggagga gtggtcgag tggtaggcn gcagcagctg 180
gccaggctac gtgcgcccc tgccccccgc cgcacgaga gcccgcagt ggccgngccc 240
gctacagncg nncgct                                     256
```

```
<210> 353
<211> 592
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc feature
<222> (35)
<223> n equals a,t,g, or c
```

```
<220>
<221> misc feature
<222> (54)
<223> n equals a,t,g, or c
```

```
<220>
<221> misc feature
<222> (93)
<223> n equals a,t,g, or c
```

```
<220>
<221> misc feature
<222> (277)
<223> n equals a,t,g, or c
```

```
<220>
<221> misc feature
<222> (480)
<223> n equals a,t,g, or c
```

```
<220>
<221> misc feature
<222> (485)
<223> n equals a,t,g, or c
```

```
<220>
<221> misc feature
<222> (522)
<223> n equals a,t,g, or c
```

```
<220>
<221> misc feature
<222> (545)
<223> n equals a,t,g, or c
```

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<400> 353
ggttccttc cagctgttg aagcattgta ctttnggtct tcatgataaa tctngctgct 60
```

295

```

gctcactcgt tgggtccgtg ccacctttaa aanctgtaac actcaccgag aaggtctgca 120
acttcactcc tggggccagc aagaccacga gtgcaccgag aggaatgaac aactctggac 180
acaccatctt taagaaccgt aatactcacc gcaagggtct gcaacttcat tcttgaagtc 240
agtgaggcca agaaccatc aattccgtac acatttnggt gactttgaag agactgtcac 300
ctatcaccaa gtggtgagac tattgccaag cagtgaagct attgccaagt ggtgagacca 360
tcaccaagcg gtgagactat cacctatcgc caagtgggtc taagtgtgaa cgtgaagtcc 420
ccagccctgc tgctgagcca gttgctgccc tacatggaga acaagaaggg tgctgtcatn 480
ctggnetctt ccattgcagc ttataatcca gtagtggcgc tnggtgtcta caatgtcagc 540
aaganagagc tgctgggggc tcactagaac actggcattg ggcttggccc cc 592

```

<210> 354

<211> 539

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (223)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (225)

<223> n equals a,t,g, or c

<400> 354

```

cacnaacct cactaaaggg aacaaaagct ggagctccac cgcggtgacg gccgctctag 60
aactagtgga tcccccgggc tgcaggaatt cggcacgagt cgtctcaggc tcgtagttcg 120
ccttcaacat gccggaacca gcgaagtccg ctcccgcgcc caagaagggc tcgaagaaag 180
ccgtgactaa ggcgcagaag aaggacggca agaagcgcaa ggnanccgca aggagagcta 240
ctccgtatac gtgtacaagg tgctgaagca ggtccacccc gacaccggca tctcctctaa 300
ggccatggga atcatgaact ccttcgtcaa cgacatcttc gaacgcacgc cgggtgaggc 360
ttcccgcctg gcgcattaca acaagcgctc gaccatcacc tccagggaga tccagacggc 420
cgtgcgcctg ctgctgcccg gggagttggc caagcacgcc gtgtccgagg gcaccaaggc 480
cgtcaccaag tacaccagcg ctaagtaaac ttgccaagga gggactttct ctggaattt 539

```

<210> 355

<211> 435

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (296)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (299)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (396)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (419)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (421)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (422)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (424)
<223> n equals a,t,g, or c

<400> 355
gcttcgctca cctgcccaag agtacctttg tggttgatga atttaagcgc aagtactcca 60
atgaggacac actctctgtg gcactgccat atttctggga gcactttgat aaggacggct 120
gggtccctgtg gtactcagag tatcgcttcc ctgaagaact cactcagacc ttcattgagct 180
gcaatctcat cactggaatg ttccagcgac tggacaagct gaggaagaat gccttcgcca 240
gtgtcatcct ttttggaaac aacaatagca gctccatttc tggagtctgg gtcttncng 300
gccaggagct tgcctttccg ctgagtccag attggcaagt ggactacgaa gtcatacaca 360
tggcggaac tggatctggc aagcgaggag acccanacgc tggttcgaga gtacttttnc 420
nngngagggg gcctt 435

<210> 356
<211> 502
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (21)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (168)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (239)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (243)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (252)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (275)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (288)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (292)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (298)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (316)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (324)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (328)
<223> n equals a,t,g, or c

<220>
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<222> (339)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (348)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (364)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (372)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (386)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (390)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (393)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (397)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (403)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (413)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (417)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (419)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (420)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (425)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (426)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (430)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (437)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (440)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (442)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (445)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (449)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (452)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (457)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (458)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (459)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (461)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (476)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (478)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (485)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (497)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (499)
<223> n equals a,t,g, or c

<400> 356
aattcggcac gagagggagt ntgagcaagg ggtgtacacc tgcacagcac agggcatttg 60
gaagaatgaa cagaagggag agaagattcc tcggtgcttg ccagtttgtg ggaagcccgt 120
gaaccccgtg gaacagaggc agcgcatcat cggagggcaa aaagccangg ggatagtggg 180
ggcgtttttg cagtaaggga cccgaacact gatcgctggg tggccacggg catcgtgtnc 240
ctngggcatc gngtgcagca gggccttatg gcttnttaca ccaaagtnc cnaacttncg 300
tggccttggg tcaagnnaga cctngganca ggaggactnc cgccccanca ttacttaggt 360
tccnaatcca gngagcagtt tcgcanaaan canccanaca cancttcccc ctntttngnn 420
accnncagn gtctctnttn anatncctnc tngcacnnna ncccacaacc ccccnccnc 480
cccnccccc ccccnccnc cc 502

<210> 357
<211> 440
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (45)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (236)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (262)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (293)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (300)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (316)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (339)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (360)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (362)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (378)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (387)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (389)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (402)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (407)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (418)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (426)
<223> n equals a,t,g, or c

<400> 357
aatatatcga acagtcaggt taacaggctg cggcattttg tccgngccgg gcttcgctca 60
ctgttcaggc cggagccaca gaccgccgtt gaatgggcgg atgctaatta ctatctcccg 120
aaagaatccg cataccagga agggcgctgg gaaacactgc cctttcagcg ggccatcatg 180
aatgcgaatg ggcagcgact acatccgtga gtggaatgtg gtgaagtttg cccgtntcgg 240
ttattccaaa atgctgctgg gngtttatgc ctactttata gggcataagc agnggaacan 300
ccttatttgg tttccncagg atggtggatg cccgagaant ttttgaaaaa cccacgttgn 360
gncgattatt tcgggganat ttccgngnt gttgggggtt gncgccntgg gttttggnaa 420
aaaganccgg gtaaaagggt 440

<210> 358
<211> 234
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (16)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (46)
<223> n equals a,t,g, or c

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<220>
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<222> (208)
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<220>
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<222> (230)
<223> n equals a,t,g, or c

<400> 358
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tgtgatgaag gagatgggag gccatcacat tntagtcctc tttttgctca aggggggcta 120
taaatttttt gctgacctgc tggattacat caaaggactg antagnaaat agtgnataga 180
tccattcctc atgaactgtg gatttttngc agatctgaag agctattgtg atga 234

<210> 359
<211> 668
<212> DNA
<213> Homo sapiens

<220>
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<220>
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<220>
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<220>
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<220>
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305

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<220>
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 <222> (559)
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<220>
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 <222> (579)
 <223> n equals a,t,g, or c

<220>
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 <223> n equals a,t,g, or c

<220>
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<220>
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 aagctggtac gcctgcaggt accggtccgg aattcccggg tcgaccacg cgtccggggg 120
 gtttgaggta cataagaaaa atgtaagggg tgaattcact tattatgaaa tacaagataa 180
 tacaggggag atggaagtgg tgggtgcatgg acgactgacc acaatcaact gtgaggaagg 240
 agataaactg aaactcacct gctttgaatt ggcaccgaaa agtgggaata ccgngagatt 300
 gagatctgta attcatagtc acatcaaggt catcaagacc aggaaaaaca agaaagacat 360
 actcaatcct gattcaagta tggaaacttc accagacttt ttcttctaaa atctggatgt 420
 cattgacgat aatgtttatg gagataaggt ctaagtgcct aaaaaaatgt acatatacct 480
 gggttgaaata caacactata catacacacc ancatatata ctagcttggt aatcctatgg 540
 aaatggggta tntggagnnc ttttttaatt tttcatagnt ttttttnat aanaatggca 600
 ttttttgat ctacaacttc tatgatttga aaaaatacct taacccttat cttttttgng 660
 aaaaaana 668

<210> 360
 <211> 401
 <212> DNA
 <213> Homo sapiens

<400> 360
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cgctaaaaat gcggatatca gtggcagtgt gaatgcgaac tccgggacgc tcagtaatgt 120
gacgatagct gaaaactgta cgataaacgg tacgctgagg gcggaaaaaa tcgtcgggga 180
cattgtaaag gcggcgagcg cggcttttcc gcgccagggtg gaaagcagtg tggactggcc 240
gtcaggtagc cgtactgtca cgtgaccga tgaccatcct tttgatcgcc agatagtggg 300
gcttccgctg acgtttcgcg gaagtaagcg tactgtcagc ggccaggacaa cgtattcgat 360
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<210> 361
<211> 273
<212> DNA
<213> Homo sapiens

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<220>
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<222> (189)
<223> n equals a,t,g, or c

<220>
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<222> (236)
<223> n equals a,t,g, or c

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tgagccgtaa ttatcatctg cgcgggcgta ttctgcagggt gccgtcgaac tataaccgcg 120
agacgcggca atacagcggg atctgggacg gaacgnntaa accggcatac agcaacaaca 180
tggcctggng tctgtgggat atgctgaccc atccgcgcta cggcatgggg aaacgncttg 240
gtgcggcgga tgtggataaa tgggcgctgt atg 273

<210> 362
<211> 248
<212> DNA
<213> Homo sapiens

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<220>
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<222> (37)
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<220>
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<222> (145)
<223> n equals a,t,g, or c

<220>
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<222> (161)
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<220>
<221> misc feature
<222> (185)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (194)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (210)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (218)
<223> n equals a,t,g, or c

<400> 362
cgctngtcgg gcgagcgatg atgcggaagg ttacctngat nttttcaaag gnaagataac 60
cgaatcccat ctngcaagg agctgctgga aaaagtcgag ctgacggagg ataacgccag 120
cagactggag gagttttcga aagantggaa ggatgccagt nataagtgga atgccatgtg 180
ggctntcaaa attnagcaga ccaaagacgn caaacgantt ttattctgct atttagtagt 240

aagatcag

248

<210> 363

<211> 149

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (131)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (137)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (144)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (145)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (147)

<223> n equals a,t,g, or c

<400> 363

tgccggactt tcatacgtgag gatgactggt ggcgtaacgg ccagaatctc tatctggata 60

atctggaggc gacggggctg tatcaggtgc cgttgctcagc ggcacagccg ggcgatgtgc 120

tgctgtgctg ntttgntca tcannngc 149

<210> 364

<211> 352

<212> DNA

<213> Homo sapiens

<220>

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<220>

<221> misc feature

<222> (93)

<223> n equals a,t,g, or c

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<221> misc feature
<222> (196)
<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (322)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (325)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (338)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (340)
<223> n equals a,t,g, or c

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gcanaaagaa aatggcacag taacagctgc caatgccagt acactgaatg atggagcagc 60
tgctctggtt ctcattgacg cagatgcagc gangaggctc aatgttacac cactggcaag 120
aatagtagca tttgctgacg ctgctgtaga acctattgat tttccaattg ctcctgtata 180
tgctgcatct atggtnccta aagatgtggg attgaaaaaa gaagatattg caatgtggga 240
agtaaatgga agccttttagt ctggtgtgac tagcaaacat taaaaatggt ggagattgga 300
tccccaaaaa gtgaatatnc anggnaggag ctgtttcncn ggggacatcc ca 352

<210> 365
<211> 272
<212> DNA
<213> Homo sapiens

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<220>
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<222> (42)
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<220>
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<222> (44)
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<222> (80)
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<222> (91)
<223> n equals a,t,g, or c

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<222> (116)
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<220>
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<222> (132)
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<222> (145)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (190)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (226)
<223> n equals a,t,g, or c

<220>
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<222> (242)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (260)

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<220>

<221> misc feature

<222> (261)

<223> n equals a,t,g, or c

<400> 365

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ggcttggtgcc gctgctggan tgacagcctt ncgaggcttt gctgtctcgg cacggnaggt 120
ctggcaaacc anggacagac caggnacatg ggaccaaagc cggaacctcc tgctcaacgg 180
gaagtcctan cccaccaaag tgcgcctgat ctgggggggc tccctncccc cagtcaagcg 240
gncggcggat gaactggatn nacgccccgg at 272
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<210> 366

<211> 254

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (23)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (192)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (208)

<223> n equals a,t,g, or c

<220>

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<222> (209)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (236)

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<222> (244)

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<400> 366

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ggctctacta ggactcacta tanggaaagc tggtagcct gcaggtagcg gtccggaatt 60
cccggtcgga cccacgcgtc cgcttctctg cctagaaggg ataataattat cactcttcgt 120
tataataaca atcaccatct taattaacca ccttacatta gccagcataa cccctatcat 180
ccttcttgta tntgcagcct gtgaagcnc actggggctt atccctttta gttatnatct 240
caantacata cgga 254
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<210> 367

<211> 185

<212> DNA

<213> Homo sapiens

<400> 367

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gattggattc gacaacaaaa aagacctgct tatctcggtg ggcgatttgg ttgatcgtgg 60
tgcagagaac gttgaatgcc tggaattaat cacattcccc tggttcagag ctgtacgtgg 120
aaacctgag caaatgatga ttgatggctt atcagagcgt ggaaacgtta atcactggct 180
gctta 185
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<210> 368

<211> 458

<212> DNA

<213> Homo sapiens

<220>

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<220>

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<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (15)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (27)

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<220>
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<222> (170)
<223> n equals a,t,g, or c

<220>
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<220>
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<220>
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<220>

<221> misc feature

<222> (433)

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<400> 368

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ccggagttag ccttgaacgc ctggacctgg acctcacagc tgacagccag ccacccgtct 120
tcaaggtctt cccaggcagt accactgagg actacaacct tattgttatn gaacgtggcg 180
ctgccgctgc acnaccggcc agccagggac tgcgcctgca ggaacccctg gngccccacc 240
cctggntggn atggccattg tcaaggagga ggagacggag gctgccattg gagccctcc 300
tactgccact gagggncctg agaccaaacc tgtgttatn gctcttgagg agggtcctgg 360
tgctgagggt tcccggctgg actcactagt ggcanaacna ctcnnggctgg aagtngtagc 420
tctgaggggac tcngcccagc tgttggccgg gacctgat 458
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<210> 369

<211> 288

<212> DNA

<213> Homo sapiens

<220>

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<222> (15)

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<220>

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<222> (17)

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<222> (47)

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<222> (56)

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<220>
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<222> (225)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (239)
<223> n equals a,t,g, or c

<400> 369
gcgctggagc tgctnngca ctgcggcgtg tgcagagagc gcctgcnacc cgaganggag 60
ccccgcctgc ngccctgttt gcactcggcc tgtagtgcc tcntagggcc cgcngccccg 120
ccgccgcaaa cagctcgggg gacggcgggg cggcgggga cggcaccgtg gtggactgtc 180
ccgtgtgcaa gcaacagtgc ttctccaaag acatcgtgga gaatnatttc atgcgtgana 240
gtggcagcaa ggctgccacc gacgcccagg atgcgaacca gtgctgca 288

<210> 370
<211> 292
<212> DNA
<213> Homo sapiens

<220>
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<220>
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<222> (53)
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<220>
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<220>

<221> misc feature
<222> (101)
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<220>
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<222> (141)
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<220>
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<222> (263)
<223> n equals a,t,g, or c

<400> 370
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ntcctccgcc gccgcggact ccggcagctt tatcgccaga ntccctgaac tctcgctttc 120
tttttaatcc cctgcatcgg ntcaccggcg tgccccacca tgtcagacgc agccgtagac 180
accagctccg aaatcaccac caaggactta aaggagaaga aggaagtttt ggaaagaggc 240
agaaaatgga agagacggcc ctnccttaacg gggaatgcta atttagggaa at 292

<210> 371
<211> 477
<212> DNA
<213> Homo sapiens

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<222> (276)
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<220>
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<222> (313)
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<220>
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<222> (342)
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<220>
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317

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<222> (427)
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<222> (448)
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<220>
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<222> (451)
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tggttccaag cataaaagaa cggacagatc aattttatgt tgtttacgaa aaggagaatc 120
tggccagtca tggcaagggt taacaaaaga aaggggcaaag cttaattggc ttagtgctga 180
cttcaataat tgggaaagac tgggaagatg attcaaatga agacatgtct aattttgaat 240
cgtttctctg aggattcaca agacagtgat gatggnaaaa atgccagatc tgggagtaag 300
ggaatattgt ccntcacctg ggtttttgag gaaaggaaaa tnaactttct ctggcaagggt 360
tttcataat ttngaggaa ttccccgagt ttgtagcnc ctaaagggn gttatgctcg 420
tatttgnccc actntaaccc ctttttnnca nccggtttgt ttttttaaaa gggcttc 477

<210> 372
<211> 443
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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<220>
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<220>
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<222> (171)
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<220>
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<222> (222)
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<220>
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<222> (293)
<223> n equals a,t,g, or c

<220>
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<222> (314)
<223> n equals a,t,g, or c

<220>
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<222> (329)
<223> n equals a,t,g, or c

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<222> (335)
<223> n equals a,t,g, or c

<220>
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<222> (340)
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<220>
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<222> (351)
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<220>
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<220>
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<222> (373)
<223> n equals a,t,g, or c

<220>
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<222> (407)
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<220>
<221> misc feature
<222> (411)
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<220>
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<222> (426)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (430)

<223> n equals a,t,g, or c

<400> 372

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agaaganatc cttnaccctt gtaggaatgt ttttgaaact aaatttnatg aacgtnaaat 120
ttncagtggt ttattatgaa cttccttgtc gaagttgaaa ggtgaacaac nctnatattg 180
caaataccgt agagcttcag agtgcaagat tctccactgn angttgggca ttcacaaatg 240
ttggatcttt cccaccgtgg gatgaagggg tcagaggcat tgcacccaaa atnaccggg 300
tgaacatacc cagnccaaag cccaggggna cattnatcgn ggacaggccc nccagaattt 360
ggcntgttct ttncagttg gtaggtgtgg aacttggggg tgaattnatt ncttaaccga 420
attnnccgn ttccttaacc gag 443
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<210> 373

<211> 464

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (20)

<223> n equals a,t,g, or c

<220>

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<400> 373

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acgttttcaa cggaggtact atactggcaa ttgctggaga agattttgca attgttgctt 180
ctgatactcg attgagtga gggttttcaa ttcatacgcg ggatagcccc aaatnttaca 240
aattaacaga caaaacagtc attggatgca gcggttttca tggagactgt cttacgctga 300
caaagattat tgaagcaaga ctaaagatgt ataagcattc caataataag gccatgacta 360
cgggggcaat tgctgcaatg ctgtctacaa tcctgtattc aaggcgcttc tttccatact 420
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<210> 374

<211> 369

<212> DNA

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<400> 374
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ctggcaattg ctggagaaga ttttgcaatt gttgcttctg atactcgatt gagtgaagg 180
ttttcaattc atacgcggga tagcccaaa tgttgncna ntaacagaca aaacagtc 240
tggaatgcagc ggttttcatg gagactgtct tacgctgaca aagattattg aagcaagact 300
aaagatgtat aagcattcca ataataaggc cntgactacg gggggcaatg ctggcangcn 360
gtactacan 369

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tctgctctc tttttcgtg agagctatcc cttcaccacg gaggaagtc tatctctcac 180
aaattccggg actggtaaac atggcgctgt acgtttcgcc gattgtttcc ggtgaagggt 240
atcccgttnc cctggcggnr tccacctntg aatttaaggc cgggataatg tcnaagcccg 300
aagcatgnaa gtg 313

<210> 376
<211> 375
<212> DNA
<213> Homo sapiens

<400> 376
cgggttcagg tgaccacgaa ggcggcaaag gcgacggaat ggaggagggt cctcacgact 60
gtccaggggc cgacagcgcc caggcgggca gaggggcttc atgtcaggga tgccccaacc 120
agcggctgtg cgcttctgga gcgggggcca ctccggacac ggctatagag gaaatcaaag 180

agaaaatgaa gactgtaaaa cacaaaatct tggattgtc tgggaaaggc ggtgttggga 240
aaagcacatt cagcgccac cttgcccatt gcctagcaga ggatgaaaac acacagattg 300
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agcaggttca ccaga 375

<210> 377
<211> 434
<212> DNA
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327

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tgaagtgcac acagacacca acaagnttgc ngaatttctg nangcagtgc tgtgccctcc 180
caggtagcccc aanctggcag ctctgaaccc tnantccaac acagctgngc tgganatatt 240
tgncaaattn tctgcctaca tnnnnanttc aaaccacagna ctcaatgaca atctggagaa 300
nggactcctg aaagccctgn acgttttagn caattantta acatcccccc nctcagaaga 360
agtggatgan accagtgtg nagtgaaggt gtctctcaga agaagttnt ggatagcacg 420
agctcaccct gggg 434
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<211> 506

<212> DNA

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<222> (294)

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<221> misc feature

<222> (389)

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<220>
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 tatgcgactt accgcagcaa aaataaaggg aaagataagc gctcaataaa cctgtctgtt 120
 ttccttaatt cnttgctggc tgataatcat cacctgcagg ttggctccaa ttatttgtat 180
 attcataaaa tcgatggaaa aacttttctc tttacaaaaa caaatgacaa gagtctggtt 240
 cagaagataa atcgctctaa agcttcagtt gaagatatta agaacagcct cgtngatgac 300
 ggaatcattg ggattcccat cttttttggt tggtgaaggc gacaccattg gtttttgcca 360
 gaactgnttt tcgggncggc cacatncgnt tttgacaggc ttttttaatc ggggaaggga 420
 ntgtccttaa ggcgtggggn gcngttcagt tggggccctg ttggggggac cnccaaggng 480
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<210> 379
<211> 550
<212> DNA
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<222> (6)
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<220>
<221> misc feature
<222> (9)
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ctagaactag tggatccccc gggctgcagg aattcggcac gaggccatcc agactgagga 120
agaccgggaa acttaggggc cacgtgagcc acggccacgg ccgcataggc aagcaccgga 180
agcaccggcg cgccgcgggt aatgctggtg gtctgcatca ccaccggatc aacttcgaca 240
aataccaccc aggctacttt gggaaagtgt gtatgaagca ttaccactta aagaggaacc 300
agagcttctg cccaactgtc aaccttgaca aattgtggac ttgggtcagt gaacagacac 360
gggtgaatgc tgctaaaaac aagactgggg ctgctcccat cattgatgtg gtgcgatcgg 420
gctactataa agttctggga aagggaaagc tcccaaagca gcctgtcatc gtgaaggcca 480
aattcttcag cagaagagct gaggagaaga ttaagagtgt tggggggggc tgtgtcctgg 540
tggttgaag 550

<210> 380
<211> 573
<212> DNA
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<222> (10)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (160)
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ccgctctaga actagtggat cccccgggct gcaggaattc ggcacgagcg caaagaagg 120
tggcgagaag aaaaagggcc gttctgccat caacgaaggn taacccgaga atacaccatc 180
aacattcaca agcgcattcca tggagtgggc ttcaagaagc gtgcacctcg ggcactcaaa 240
gagattcgga aatttgccat gaaggagatg ggaactccag atgtgcgcat tgacaccagg 300
ctcaacaaag ctgtctgggc caaaggaata aggaatgtgc cataccgaat ccgtgtgcgg 360
ctgtccagaa aacgtaatga ggatgaagat tcaccaaata agctatatac tttggttacc 420
tatgtacctg ttaccacttt caaaatttct gtgctaaaca gtgttacagt cgccaagagc 480
ccataaaggg agccctcctg gaagtggatg aggccttggg tctcggtctt tcattgcttc 540
ctgagctgca gcagatgcct ttacaaccaa gct 573

<210> 381

<211> 531

<212> DNA

<213> Homo sapiens

<220>

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<222> (5)

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<220>

<221> misc feature

<222> (8)

<223> n equals a,t,g, or c

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tagaactagt ggatcccccg ggctgcagga attcggcacg aggcggcggt ggcggcttgt 120
gcagcaatgg ccaagatcaa ggctcgagat cttcgcggga agaagaagga ggagctgctg 180
aaacagctgg acgacctgaa ggtggagctg tccagctgc gcgtcgccaa agtgacaggc 240
ggtgcggcct ccaagctctc taagatccga gtcgtccgga aatccattgc ccgtgttctc 300
acagttatta accagactca gaaagaaaac ctcaggaaat tctacaaggg caagaagtac 360
aagcccctgg acctgcggcc taagaagaca cgtgccatgc gccgccggct caacaagcac 420
gaggagaacc tgaagaccaa gaagcagcag cggaaggagc ggctgtaccc gctgcggaag 480
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<210> 382

<211> 300

<212> DNA

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accatccgca gagatgcccc tgctggccgc aaagtgggtc tcattgctgc nngcnggant 180
ggangtctcn ggggaaccaa gantgtgcag gagaaagaga actagtgtctg agggcctcaa 240
taaaagtttgt gtttatgcc aaaaaaaaaa naaaaaaaaa aaaaaaaaaa annaaagagn 300

<210> 383

<211> 475

<212> DNA

<213> Homo sapiens

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<222> (363)

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ccggggccga gccgcggac tcgcgnaggc aaggccgagg ataaggagtg gatgcccgtc 180
accaagttgg gccgcttgg caaggacatg aagatcaagt ccctggagga gatctatctc 240
ttctccctgc cattaagga atcagagatc attgattctt cctgggggct ctctcaagga 300
tgagttttga agatatgcca tgcagaagca gaccctgccg gccacgcacc agttcaagca 360
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<210> 384
<211> 127
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angagattaa ncagagacac aggcaattgt atgtcagcag ctngatttaa cccacctaaa 120
aggngcgg 127

<210> 385

<211> 317

<212> DNA

<213> Homo sapiens

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<220>
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<222> (316)
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gagaccagtg agaaacgccc cttcatgtgt gcttaccag gctgcaataa gagatatttt 120
aagctgtccc acttacagat gcacagcagg naagcacact ggtgagaaac cataccagtg 180
tgacttnaag gactgtgaac gangttttct cgttcagacc agctcaaaag ncaccaaagg 240
aggacataca ggtgtgaacc attnccagtg taaaattggt cagcgaaatt ctcccgtcc 300
gaccaacnga ngaccna 317

<210> 386
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 <222> (407)
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 <222> (427).
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 cggcagcgcc atgagactcc tccccgctt gctgctgctt ctcttactcg tgtccctgc 180
 cactgtcttg ttccgaggcg gccccagagg ctgttagca gtggcacaag atcttacaga 240
 ggatgaagaa acagtagaag attccataat tgaggatgaa gatgatgaag ccgangtaga 300
 agaagatgaa nccacagatt ttgtagaaga taaagaggaa gaagatgtgt ctggtgaanc 360
 tgaaacttta ccgagtgcag atacnactat actgttttta aaggngnaga tttccgcca 420
 ataacantgt gaa 433

<210> 387
 <211> 407
 <212> DNA
 <213> Homo sapiens

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<220>

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<222> (376)

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<220>

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<222> (407)

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<400> 387

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ggtgacgggt ctgtacgacg tgcaggcttt caagtttggg gacttcgtgc tgaagagcgg 120
gctttcctcc cccatctaca tcgatctgcg gggcatcgtg tctcgaccgc gtcttctgag 180
tcagggttgc gatattttat tccaaactgc ccaaaatgca ggcacagtt ttgacaccgt 240
gtgtggagtg ccttatacag ctttgccatt ggctacagtt atctgttcaa ccaatcaa 300
tccaatgctt attanaagga aagaaacaaa ggattatgga actaagcgtc ttgtanaang 360
aatattaatc canganaaac tgtttaatca ttgaaatggt gtcccan 407
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<210> 388

<211> 244

<212> DNA

<213> Homo sapiens

<220>

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<220>

<221> misc feature

<222> (221)

<223> n equals a,t,g, or c

<400> 388

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tcaggcgggc catttttatt gctgtgttgc gctgtaattc ttctatttct gatgctgaat 120
caatgatgtc tgccatcttt cattaatccc tgaactgttg gttaatacgc ttgaggggtga 180
atgcgaataa taaaaaagga gcctgtagct ccctnatgat nttgcttttc atgttcacg 240
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ttcc

244

<210> 389

<211> 239

<212> DNA

<213> Homo sapiens

<220>

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<220>

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<222> (21)

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<220>

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<222> (55)

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<220>

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<222> (64)

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<222> (71)

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<220>

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<222> (116)

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<220>

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<222> (128)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (163)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (185)

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<220>
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<222> (196)
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<222> (202)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (205)
<223> n equals a,t,g, or c

<400> 389
nggactggcg tcagacgtcg nattccggcg cccacggctcg gcttaaaccg tggtncaatc 60
ctgncgcccg ncgtgatgcc agggaagaca gggcgacctg gaagtccaac tacttnctta 120
agatcatnca acgtattggg atgattatcc taaaatgggt tcnattgggt ggtagcgagt 180
acganatggt ggggcntcct anagntagta tggcgagcta gagtcccggc taatgttcc 239

<210> 390
<211> 382
<212> DNA
<213> Homo sapiens

<220>
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<220>
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<222> (54)
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<220>
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<222> (69)
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<222> (102)
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<220>
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<222> (103)
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<220>
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<220>
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<223> n equals a,t,g, or c

<220>
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<222> (169)
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<220>
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<222> (221)
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<220>
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<220>
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<220>
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<222> (345)
<223> n equals a,t,g, or c

341

<220>
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<222> (346)
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<220>
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<220>
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<222> (374)
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<400> 390
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cgcgctgcnc gcacactgag gccgcccggg acaaagcccg gnntcggngc gacctttggt 120
cccggntcga gtgagcgagc gagcgcgagc agagggagtg gccaaactna tcactagggg 180
ttccttgtag tnaatgatta acccgccatg ctacttngnc nacgtagcca tgggntacca 240
agctcgagct ctctagactc gacgcgcgta atacgactca ctatagggcg aatttgagct 300
ccaccgcggt tgcggccgct ctactagagt cgacctcatg gnttncccc gaaaccgcgn 360
aacaccgcgt gacncgcct ta 382

<210> 391
<211> 375
<212> DNA
<213> Homo sapiens

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<220>
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<222> (7)
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<220>
<221> misc feature
<222> (48)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (70)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (104)
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<220>
<221> misc feature
<222> (117)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (138)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (146)
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<220>
<221> misc feature
<222> (159)
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<220>
<221> misc feature
<222> (208)
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<220>
<221> misc feature
<222> (223)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (261)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (269)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (275)
<223> n equals a,t,g, or c

<220>
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<222> (279)

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<220>

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<222> (299)

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<220>

<221> misc feature

<222> (351)

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<220>

<221> misc feature

<222> (366)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (370)

<223> n equals a,t,g, or c

<400> 391

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cgggtgcagn tgccaggggtg gcctgagcga tctacggatg ggcngtatgg agtggangag 120
acgagatgcg ggtgttanag cagggnctga ccggagtgnс acacatgagt gtcaggtgca 180
ggtagtccga gtcggcgaca tgagcctnga gtagagtcат cantcgatga gatctggagg 240
caactggcga gcaagaccgt ntgggtgcant gtcantcang ctgttgсagg tgagagcant 300
gcactcgtcg agtggcgaga cagatcaatc tctgttagcg ggtggagggt ncactcgсgс 360
tgtgngggtн cactg 375
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<210> 392

<211> 121

<212> DNA

<213> Homo sapiens

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<222> (3)

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<220>

<221> misc feature

<222> (9)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (13)

<223> n equals a,t,g, or c

<220>
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<220>
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<220>
<221> misc feature
<222> (113)
<223> n equals a,t,g, or c

<220>
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<222> (118)
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<220>
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<222> (120)
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<400> 392
gantcatcng agngtgtgga ttgagccgc cgcatttttt aaccctaaat ctcganatgc 60
atcgtgnttc ctgtccattg gactgtaagg ttatgtagg catcttgga acnatggan 120
a 121

<210> 393
<211> 83
<212> DNA
<213> Homo sapiens

<220>
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<223> n equals a,t,g, or c

<220>
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<222> (66)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (70)
<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (73)

<223> n equals a,t,g, or c

<400> 393

ggcagagaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60
aaaanncccn ggngggggcc ccc 83

<210> 394

<211> 218

<212> DNA

<213> Homo sapiens

<220>

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<220>

<221> misc feature

<222> (64)

<223> n equals a,t,g, or c

<400> 394.

gtcggcgagc aangcgcccc gcacccccgc caggcgcatg tctgcacctc cgcttgccaa 60
aggnctcgg tcagcgactg gatgctcgcc atcaagggtcc agtgaagtt cttcaagagg 120
aaaggcgccc ccgccccagg cttccgcgcc cagcgctcgc cacgctcagt gcccgtttta 180
ccaataaact gagcgacccc aaaaaaaaaa aaaaaaag 218

<210> 395

<211> 83

<212> DNA

<213> Homo sapiens

<220>

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<220>

<221> misc feature

<222> (13)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (83)

<223> n equals a,t,g, or c

<400> 395

aattcggcac ngnaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aan

83

<210> 396

<211> 70

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (69)

<223> n equals a,t,g, or c

<400> 396

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aaaaaaaaana 70

<210> 397

<211> 140

<212> DNA

<213> Homo sapiens

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<220>

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<220>

<221> misc feature

<222> (74)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (93)

<223> n equals a,t,g, or c

<220>

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<222> (113)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (114)

<223> n equals a,t,g, or c

347

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<222> (115)
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<220>
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<222> (139)
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<400> 397
aatttgacca gagaacaaga ataaccggc ctcagcggcg ggttttcttn gcctcangat 60
cgcccccaaa acanataacc aattgtatth atngaaaaat aaatagatac aannnactaa 120
acatagcaat tcagatctnt 140

<210> 398
<211> 157
<212> DNA
<213> Homo sapiens

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<222> (65)
<223> n equals a,t,g, or c

<220>
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<222> (121)
<223> n equals a,t,g, or c

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<220>
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<222> (123)
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<220>
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<222> (126)
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<220>

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<400> 398
aattcggcan agctcaagca gacggggctc aaggggggta catttaataa aaggatgaag 60
atggnaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120
nnnccngggg gggnccccc ccccccttn cccctt 157

<210> 399
<211> 358
<212> DNA
<213> Homo sapiens

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<220>
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<222> (84)
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<220>
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<222> (204)
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<220>
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<222> (207)
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<220>
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<222> (302)
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<220>
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<222> (305)
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<220>
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<222> (308)

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<220>

<221> misc feature

<222> (331)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (341)

<223> n equals a,t,g, or c

<400> 399

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gcaagcgcca tatgagcctg gcgncgcca tagcgaatcc tgttgtgggc tttttggcct 120
attcccggcc ctgagtcctg ccgggatggc accgcccga taggacttcc agggttgggc 180
tgagtgggag ttcgactgct gggncctngta attctcgctt tgggggctgc tccttccagg 240
ctggggacac actggggccc gttgttcggt ctcccgtcct ccgacatctt gtctggaact 300
tncgncctngc agtttccata ggagttggag nctgtgcggc ntaatttttg tggaaaaa 358
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<210> 400

<211> 399

<212> DNA

<213> Homo sapiens

<220>

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<222> (33)

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<222> (46)

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<220>

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<222> (70)

<223> n equals a,t,g, or c

<220>
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<222> (83)
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<220>
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<220>
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<222> (169)
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<220>
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<222> (171)
<223> n equals a,t,g, or c

<220>
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<222> (213)
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<220>
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<220>
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<220>
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<220>
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<220>

<221> misc feature
<222> (245)
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<220>
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<220>
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<222> (255)
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<222> (262)
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<220>
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<222> (269)
<223> n equals a,t,g, or c

<220>
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<223> n equals a,t,g, or c

<220>
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<222> (283)
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<220>
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<220>
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<220>
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<222> (325)
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<220>
<221> misc feature

352

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<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (364)

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<220>

<221> misc feature

<222> (382)

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<400> 400

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aaaacccaan tcagagtatc canaaatcca agccagggtca aaacccaaaac gaaantntca 120
agcaatccaa atcaagtcaa aaacaaaaaac caaagtgccg gtacaggcnt nccgtgggtg 180
atcaggccac ccttccactc aaatgggagtg ggnaantncc aaagactagt nttaccaant 240
ttcanatntc cggantccaa gngcctgtnc cttcccagng ttnagccgct gnattgatcc 300
tctgtggggg cctgcnaaac gccantctgg cgagggtgttc cactgggggna attgcctacc 360
cggnagtgtc ctcaggttct gngtccctca agctggcca 399
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<210> 401

<211> 189

<212> DNA

<213> Homo sapiens

<220>

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<220>

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<222> (11)

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<220>

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<222> (162)

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<220>

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<222> (165)

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<221> misc feature

<222> (166)

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<220>

<221> misc feature

<222> (187)

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<400> 401

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naattcggca nagcaaacca caccttctct ttcttatgtc tttttactac aaactacaag 60
acaattgttg aaacctgcta tacatgttta ttttaataaa ttgatggcaa aaaaaaaaaa 120
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa anccnngggg ggggcccccc 180
ccccccntt                                     189
```

<210> 402

<211> 174

<212> DNA

<213> Homo sapiens

<220>

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<220>

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<222> (73)

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<220>

<221> misc feature

<222> (103)

<223> n equals a,t,g, or c

<220>

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<222> (107)

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<220>

<221> misc feature

<222> (130)

<223> n equals a,t,g, or c

<220>

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<222> (132)

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<220>

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<222> (146)

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<220>
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<222> (167)
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<400> 402
aattcggcan agctgaggca ggagaatcgc ttgaattcgg gaggcagagc tgagatcaca 60
cctctgacac tcnagcctgg gtgacagagc gagactccgt ctnaggnaag gaaaaaaaaa 120
aaaaaaaaan cncggggggg gccccngtnc ccaattggcc ctatagnggg tcgt 174

<210> 403
<211> 263
<212> DNA
<213> Homo sapiens

<220>
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<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (231)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (236)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (242)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (252)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (260)
<223> n equals a,t,g, or c

<400> 403
ggcanagcca acccagcagt ccttcctca gctgcctagg aggaaggac ccagctgggt 60
ctgggaccac aaggaggag actgcacccc actgcctctg ggccctggct gtgggcagag 120
gccaccgtgt gtgtcccgag taaccgtgcc gttgtcgtgt gatgccataa gcgtctgtgc 180
gtggagtccc caatgaaacc tgtggctctg cctgggcaaa aaaaaaaaaa naaaanaaaa 240
anaaagaaaa anaaaaaaaaa aaa 263

<210> 404
<211> 478
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (159)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (259)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (427)
<223> n equals a,t,g, or c

<400> 404
tcgaccacag cgtccggggg ctgcagcatg ttgctgagga gtgaggaata gttgagcccc 60
aagtctgaa gaggcggggc agccaggctg acatctgtgt ttcaagtggg gctcgccatg 120
ccgggggttc ataggtcact ggctctccaa gtgccagang tgggcagggt gtggcactga 180
gcccccccaa cactgtgccc tgggtggagaa agcactgacc tgtcatgccc cctcaaacc 240
tcctctcttg acgtgcctnt tgcaccctc ccattaggac aatcagtccc ctcccatctg 300
ggagtccct tttcttttct accctagcca ttcttggtac ccagccatct gcccaagggt 360
gccccctect ctcccatccc cctgccctcg tgggcagccc ggctggtttt gtaaatgtgg 420
gttgtgnaca gtgatttttt cttgtattta aaaaaggcca gcattgtggt tcattaaa 478

<210> 405
<211> 223
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (147)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (158)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (172)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (217)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (223)
<223> n equals a,t,g, or c

<400> 405
agacagcagg acggtggcca tggaagtcgg aatccgctaa ggagtgtgta acaactcacc 60
tgccgaatca actagccctg aaaatggatg gcgctggagc gtcggggcca tacccgctcg 120
tcgcccggcag tcgagagtgg acgggancgg cgggggcngc gcgcgcgcgc gncgtgatgg 180
tgtgcgtcgg agggcggcgg cggcggcggg ggtgtgnggt ccn 223

<210> 406
<211> 104
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (8)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (37)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (81)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (93)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (103)
<223> n equals a,t,g, or c

357

<400> 406

cccacgcntc cgccgacagc agcagcctca ccatgagtt gctgatggtc ctcagtctgg 60
cggccctctc ccagcactgc nacgcaggct ctngctgcc ctna 104

<210> 407

<211> 66

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (17)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (21)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (57)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (66)

<223> n equals a,t,g, or c

<400> 407

gccctatagt gagtctngta ncaattcact ggccgctcgtt ttacaacgtc gtgacgngga 60
aaactn 66

<210> 408

<211> 278

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (19)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (252)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (275)

<223> n equals a,t,g, or c

<400> 408

```
gggcanagca agctcctgna cctcaagtga tccacatgcc ttggttgacc aaattgctgg 60
gattacaggc atgagccaat atgaccagct caaacatctt ctttttaa at gtcagaagca 120
tgtatagtga ttatttctta ttttttcccc ctgatccat ctcaccagat gtttggtgat 180
tttataagaa ttttcaaact accagcttct ggctttgttg aacttgggat ttctgtttca 240
ctaattttct tntcctgtgc ttgtacttac tttgntgg 278
```

<210> 409

<211> 168

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (16)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (38)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (127)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (140)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (143)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (145)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (167)

<223> n equals a,t,g, or c

<400> 409

```
aataaaactc taaaangatc actataaaaa aagcaggnac gcctgcaggt accggtccgg 60
aattccccggg tcgaccacg cgtccgacgg ctgcgagaag acgacagaag ggcacggctg 120
cgagaanacg acagaagggn gcnantgaaa gaaggcgga gaaaggnt 168
```

<210> 410

<211> 415

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (307)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (347)

<223> n equals a,t,g, or c

<400> 410

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tgaataccta agatttctgt cttgggggttt ttggtgcatg cagttgatta cttcttattt 60
ttcttaccaa ttgtgaatgt tgggtgtgaaa caattaatga agcttttgaa tcatccctat 120
tctgtgtttt atctagtcac ataaatggat taattactaa ttccagttga gaccttctaa 180
ttggttttta ctgaaacatt gaggggaacac aaatttatgg gcttcctgat gatgattctt 240
ctaggcatca tgccttatag ttgtcatcc ctgatgaatg taaaattaca ctgttcacaa 300
aggtttngtc tcctttccac tgctattaat catgggcact ctcccnaaa tattatattt 360
tttctattaa aagaaaaaaaaa tggaaaaaaaaa ttacaaggca atggaaacta ttata 415
```

<210> 411

<211> 636

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (383)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (512)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (519)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (544)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (547)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (583)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (599)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (603)

<223> n equals a,t,g, or c

<400> 411

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gcagatcaga cggtggcgacc cgctgaattt aagcatatta gtcagcggag gagaagaaac 60
taaccaggat tccctcagta acggcgagtg aacagggaag agcccagcgc cgaatccccg 120
ccccgcggcg gggcgcgagg catgtggcgt acggaagacc cgctccccgg cgccgctcgt 180
ggggggccca agtccttctg atcgaggccc agcccgtgga cggtgtgagg ccggtagcgg 240
ccccgcggcg gccgggcccg ggtcttcccg ggtcgggtt gcttgggaat gcagcccaa 300
gcgggtggta aactccatct aaggctaaat ccccttgtaa atttaactgt tagtccaaag 360
aggaacagct ctttgacac tangaaaaa cttgtagag agagtaaaaa atttaacacc 420
catagtaggc ctaaaagcag ccaccaatta agaaagcgtt caagctcaac acccactacc 480
taaaaaatcc caaacatata actgaactcc tnacaccna ttggaccaat ctatcacct 540
atanaanaac taatggtagt ataagtaaca tgaaaacatt ctnccttcgca taagcctgng 600
tanattaaaa cacttgaact gaccattaac aggcca 636
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<210> 412

<211> 182

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (129)

<223> n equals a,t,g, or c

<220>

361

<221> misc feature
<222> (166)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (169)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (170)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (172)
<223> n equals a,t,g, or c

<400> 412
ccattgattt ttatcaatag tcgtattcat acggatagtc ctggtattgt tccatcacat 60
tctgaggatg ctcttcgaac tcttcaaatt cttcttccat atatcacctt aaatagtgga 120
ttgcggtant aaagattgtg cctgtctttt aaccacatca ggctcngann gntctcgtga 180
ac 182

<210> 413
<211> 387
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (157)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (253)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (323)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (349)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (351)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (364)
<223> n equals a,t,g, or c

<400> 413
tcgacccacg cgtccgccc cgcgtccgcc aagaccaccc tcctttcatt tgctagaagg 60
actcactaga ctcaggaaag ctgttaggct cacagttaca gtttattaca gtaaaaggac 120
agagattaag atcagcaaag ggaggagggtg cacagcnacg ttccacgaca gatgaggcga 180
cgggttccat ctgccctctc ccagtggagc catataggca gcacctgatt ctcacagcaa 240
catgtgacaa canccaagaa gtactgccaa tactgccaac cagagcagct tcaactcggag 300
atctttgtgt tccaganttt ttngtttgtc ttggagacag ggtctgggnc ngtttgggca 360
gacnaagagt acatggtgga gattcac 387

<210> 414
<211> 276
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (60)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (186)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (195)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (237)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (260)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (266)

<223> n equals a,t,g, or c

<400> 414

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gcaaaggtcc atactgggta cttgggtttca ttgccaccac ttagtggatg ttcagtttan 60
aaccattttg tctgctccct ctggaagcct tgcgcatagc ttactttgta attgttggag 120
aataactgct gaatttttag ctgttttgag ttgattcgca ccaactgcacc acaactcact 180
atgaanacta tttancttat ttattatctt gtgaaaagta taccatgaaa attttgntca 240
tactgtattt atcaagtatn attaanagca ctagat                                276
```

<210> 415

<211> 192

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (78)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (88)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (99)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (145)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (150)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (164)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (168)

<223> n equals a,t,g, or c

<400> 415

```
aaaagattgg actaagacac tggccatacc actggacagg gttatgttaa cacctgaaat 60
tgctgggtct tgagagancc caacgcantt ctgggagang gaccacattg gggggtaggt 120
ccacgggctt ggtgatagaa ttatntotcn atcgacttct tgantgcnat atgaactgta 180
acatttgctt ag 192
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<210> 416

<211> 439

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (7)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (9)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (64)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (406)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (417)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (421)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (431)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (434)

<223> n equals a,t,g, or c

<400> 416

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gcgagantnc gacagaaggg tacggctgcg agagacgaca gaaggggtacg gctgcgagaa 60
gacnacagaa ggggtacggct gcgagaagac gacagaaggg tacggctgcg agaagacgac 120
agaaggggtac ggctgcgaga agacgacaga aggtacggct gcgagaagac gacagaagga 180
tacggctgcg agaagacgac agaagggaga atcttagttc aactttaaat ttgcccacag 240
aaccctctaa atccccctgt aaatttaact gttagtccaa agaggaacag ctctttggac 300
actaggaaaa aaccttgtag agagagtaaa aaatttaaca cccatagtag gcctaaaagc 360
agccaccaat taagaaagcg ttcaaagctc aacaccact acccanaaaa taaaaanaaa 420
naaaaacccg nggnccgct 439
```

<210> 417

<211> 155

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (9)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (84)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (122)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (123)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (143)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (153)

<223> n equals a,t,g, or c

<400> 417

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gacatcttnt tggtttttat ttigaaacaa ttttaggct tgttccgggg gtctctgtgc 60
tgctgtact gtattgacct gttntatagg tgccttttta ttaaaaagaa aattcaaaaa 120
```

annaaaaaaaa aaattaataa aaaaaaaaaa aanca

155

<210> 418

<211> 291

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (285)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (286)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (288)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (289)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (291)

<223> n equals a,t,g, or c

<400> 418

gaaaaaagaa atccatatct taaagaaaca gctttcaagt gcctttctgc agtttttcag 60
gagcgcaaga tagatttgga ataggaataa gctctagttc ttaacaaccg acactcctac 120
aagattttaga aaaaagttta caacataatc tagtttacag aaaaatcttg tgctagaata 180
ctttttaaaa ggtattttga ataccattaa aactgctttt ttttttccag caagtatcca 240
accaacttgg ttctgcttca ataaatcttt ggaaaaacta atttnnanna n 291

<210> 419

<211> 340

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (315)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 419

Val	Xaa	Asp	Trp	Phe	Leu	Trp	Tyr	Val	Lys	Lys	Cys	Gly	Gly	Thr	Thr
1				5					10					15	

Arg	Ile	Ile	Ser	Thr	Thr	Asn	Gly	Gly	Gln	Glu	Arg	Lys	Phe	Val	Gly
			20					25						30	

Gly	Ser	Gly	Gln	Val	Ser	Glu	Arg	Ile	Met	Asp	Leu	Leu	Gly	Asp	Arg
		35					40						45		

Val	Lys	Leu	Glu	Arg	Pro	Val	Ile	Tyr	Ile	Asp	Gln	Thr	Arg	Glu	Asn
	50					55					60				

Val	Leu	Val	Glu	Thr	Leu	Asn	His	Glu	Met	Tyr	Glu	Ala	Lys	Tyr	Val
65					70					75					80

Ile	Ser	Ala	Ile	Pro	Pro	Thr	Leu	Gly	Met	Lys	Ile	His	Phe	Asn	Pro
			85						90					95	

Pro	Leu	Pro	Met	Met	Arg	Asn	Gln	Met	Ile	Thr	Arg	Val	Pro	Leu	Gly
			100					105						110	

Ser	Val	Ile	Lys	Cys	Ile	Val	Tyr	Tyr	Lys	Glu	Pro	Phe	Trp	Arg	Lys
		115					120						125		

Lys	Asp	Tyr	Cys	Gly	Thr	Met	Ile	Ile	Asp	Gly	Glu	Glu	Ala	Pro	Val
	130					135					140				

Ala	Tyr	Thr	Leu	Asp	Asp	Thr	Lys	Pro	Glu	Gly	Asn	Tyr	Ala	Ala	Ile
145					150					155					160

Met	Gly	Phe	Ile	Leu	Ala	His	Lys	Ala	Arg	Lys	Leu	Ala	Arg	Leu	Thr
			165						170					175	

Lys	Glu	Glu	Arg	Leu	Lys	Lys	Leu	Cys	Glu	Leu	Tyr	Ala	Lys	Val	Leu
			180					185					190		

Gly	Ser	Leu	Glu	Ala	Leu	Glu	Pro	Val	His	Tyr	Glu	Glu	Lys	Asn	Trp
		195					200						205		

Cys	Glu	Glu	Gln	Tyr	Ser	Gly	Gly	Cys	Tyr	Thr	Thr	Tyr	Phe	Pro	Pro
	210					215					220				

Gly	Ile	Leu	Thr	Gln	Tyr	Gly	Arg	Val	Leu	Arg	Gln	Pro	Val	Asp	Arg
225				230						235					240

Ile	Tyr	Phe	Ala	Gly	Thr	Glu	Thr	Ala	Thr	His	Trp	Ser	Gly	Tyr	Met
			245						250					255	

368

Glu Gly Ala Val Glu Ala Gly Glu Arg Ala Ala Arg Glu Ile Leu His
 260 265 270

Ala Met Gly Lys Ile Pro Glu Asp Glu Ile Trp Gln Ser Glu Pro Glu
 275 280 285

Ser Val Asp Val Pro Ala Gln Pro Ile Thr Thr Thr Phe Leu Glu Arg
 290 295 300

His Leu Pro Ser Val Pro Gly Leu Leu Arg Xaa Ile Gly Leu Thr Thr
 305 310 315 320

Ile Phe Ser Ala Thr Ala Leu Gly Phe Leu Ala His Lys Arg Gly Leu
 325 330 335

Leu Val Arg Val
 340

<210> 420

<211> 111

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (48)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 420

Thr Arg Asp Leu Val Ser Phe Ile Ser Gly Ile Arg Leu Tyr Asn Leu
 1 5 10 15

Met Leu Ser Val Leu Arg His Lys Arg Gln Asn Val Ala Tyr Phe Arg
 20 25 30

Ile Cys Phe Phe Ile Glu Val Ser Gly Ile Leu Ser Lys Ile Val Xaa
 35 40 45

Ser Arg His Cys Ser Leu Cys Ser Ser Gly Thr Ser Cys Pro Leu Leu
 50 55 60

Ser Leu Gln Ala Thr Gly Asn Ala Ser Val Leu Val Ser Trp Arg Lys
 65 70 75 80

Ile Thr Trp Gly Glu Gly Thr Ser Cys Gly Lys Ser Lys Cys Arg Tyr
 85 90 95

Glu Met Arg Arg Leu Pro Gln Leu Lys Val Asp Lys Ser Ala Leu

369

100

105

110

<210> 421

<211> 61

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 421

Xaa Ile Trp Cys Ile Ile Cys Lys Glu Ser Lys Met Met Ser Phe Pro
1 5 10 15

Arg Gly Met Asn Leu Arg Asn Ala Phe Asp Gly Asp Val Ser Val Thr
20 25 30

Leu Cys Tyr Ser Gly Ser Ser Asn Asn Ser Lys Ala Asn Tyr Ser Lys
35 40 45

Cys Lys Ile Phe Leu Phe Pro Arg Phe Thr Phe Val Trp
50 55 60

<210> 422

<211> 51

<212> PRT

<213> Homo sapiens

<400> 422

Thr His Ala Tyr Cys Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp
1 5 10 15

Arg Ala Trp Met Gln Lys Ser His Lys Thr Arg Asn Gln His Arg Thr
20 25 30

Arg Gly Ser Cys Pro Arg Ala Asp Gly Ala Arg Arg Glu Val Leu Pro
35 40 45

Asp Lys Leu
50

<210> 423

<211> 246

370

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (71)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (101)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (117)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (147)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 423

Thr	Arg	Asn	Asp	Met	Lys	Ala	Asp	Cys	Ile	Leu	Tyr	Tyr	Gly	Phe	Gly
1				5					10					15	

Asp	Ile	Phe	Arg	Ile	Ser	Ser	Met	Val	Val	Met	Glu	Asn	Val	Gly	Gln
			20					25					30		

Gln	Lys	Leu	Tyr	Glu	Met	Val	Ser	Tyr	Cys	Gln	Asn	Ile	Ser	Lys	Cys
	35						40					45			

Arg	Arg	Val	Leu	Met	Ala	Gln	His	Phe	Asp	Glu	Val	Trp	Asn	Ser	Glu
	50					55					60				

Ala	Cys	Asn	Lys	Met	Cys	Xaa	Asn	Cys	Cys	Lys	Asp	Ser	Ala	Phe	Glu
65					70					75					80

Arg	Lys	Asn	Ile	Thr	Glu	Tyr	Cys	Arg	Asp	Leu	Ile	Lys	Ile	Leu	Lys
			85						90					95	

Gln	Ala	Glu	Gly	Xaa	Gly	Met	Glu	Lys	Leu	Thr	Pro	Ile	Gly	Asn	Trp
		100						105					110		

Ile	Asp	Ser	Trp	Xaa	Gly	Lys	Gly	Ala	Ala	Lys	Leu	Arg	Val	Ala	Gly
		115					120					125			

Val	Val	Ala	Pro	Thr	Leu	Pro	Arg	Glu	Asp	Leu	Glu	Lys	Ile	Ile	Ala
		130				135						140			

371

His Phe Xaa Ile Gln Gln Tyr Leu Lys Glu Asp Tyr Ser Phe Thr Ala
 145 150 155 160
 Tyr Ala Thr Ile Ser Tyr Leu Lys Ile Gly Pro Lys Ala Asn Leu Leu
 165 170 175
 Asn Asn Glu Ala His Ala Ile Thr Met Gln Val Thr Lys Ser Thr Gln
 180 185 190
 Asn Ser Phe Arg Ala Glu Ser Ser Gln Thr Cys His Ser Glu Gln Gly
 195 200 205
 Asp Lys Lys Met Glu Glu Lys Asn Ser Gly Asn Phe Gln Lys Lys Ala
 210 215 220
 Ala Asn Met Leu Gln Gln Ser Gly Ser Lys Asn Thr Gly Ala Lys Lys
 225 230 235 240
 Arg Lys Ile Asp Asp Ala
 245

<210> 424

<211> 109

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (77)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 424

Asp His Trp Pro Arg Pro Glu Trp Leu Pro Cys Thr Ser Trp Arg Arg
 1 5 10 15
 Ala Ser Cys Leu Asn His Val Asn Cys His His Leu Ala Thr Pro Ala
 20 25 30
 Pro Ala Ser Ala Leu Pro Pro Phe Pro Pro Ser Trp Ser Gly Gly Tyr
 35 40 45
 Arg Ser Leu Gly Pro Thr Leu Ala Pro Leu Ser Pro Ala Ser Val Cys
 50 55 60
 Leu Thr Val Phe Pro Pro Leu Pro Gln Leu Arg Cys Xaa Pro Gln Ala
 65 70 75 80
 Trp Cys Cys Leu Gly Gly Leu Gly Glu Gly Val Cys Gly Gly Gly Arg
 85 90 95

372

Arg Val Lys Thr Glu Ala Arg Cys Gln Asn Gly Leu Glu
100 105

<210> 425

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 425

Gly Ser Glu Thr Xaa Lys Tyr Leu Val Glu Asp Lys Arg Leu Gly Leu
1 5 10 15

Tyr Thr Trp Leu Cys Thr Asp Leu Leu Ser His Ile Gly Asn His His
20 25 30

Thr Leu Gln Gly Ile Ser Phe Ile Cys Lys Met Gln Arg Leu Val Leu
35 40 45

Xaa Asn His Thr Asn Phe Phe Val Leu
50 55

<210> 426

<211> 99

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (96)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 426

Phe Gly Thr Ser Gly Asp Gly Gly Gly Ser Lys Met Ala Gln Ala Ile
1 5 10 15

Phe Glu Ala Leu Glu Gly Met Asp Asn Gln Thr Val Leu Ala Val Gln

373

20 25 30
 Ser Leu Leu Asp Gly Gln Gly Ala Val Pro Asp Pro Thr Gly Gln Ser
 35 40 45
 Val Asn Ala Pro Pro Ala Ile Gln Pro Leu Asp Asp Glu Asp Val Phe
 50 55 60
 Leu Cys Gly Lys Cys Lys Lys Gln Phe Asn Ser Leu Pro Ala Phe Met
 65 70 75 80
 Thr His Lys Arg Glu Gln Cys Gln Gly Asn Ala Pro Ala Leu Ala Xaa
 85 90 95
 Val Ser Leu

<210> 427
 <211> 55
 <212> PRT
 <213> Homo sapiens

<400> 427
 Asn Ser Asn Ser Ser Ile Phe Ser Leu Val Ser Val Lys Cys Asp Lys
 1 5 10 15
 Ser Thr Tyr Phe Lys Leu Phe Ser Ala Leu Gly Tyr Ser Ser Asn Lys
 20 25 30
 Asn Thr Asn Leu Trp Val Phe Lys Lys Thr Trp Arg Ile Asn Ser Tyr
 35 40 45
 Phe Lys Arg Ser Lys Lys Lys
 50 55

<210> 428
 <211> 54
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (41)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 428
 His Thr Leu Ser Asn Leu Glu Phe Ala Gln Lys Val Glu Pro Cys Asn

374

1 5 10 15
 Asp His Val Arg Ala Lys Leu Ser Trp Ala Lys Lys Arg Asp Glu Asp
 20 25 30
 Asp Val Pro Thr Val Pro Ser Thr Xaa Gly Glu Glu Arg Leu Tyr Asn
 35 40 45
 Pro Phe Leu Arg Val Ala
 50

<210> 429
 <211> 39
 <212> PRT
 <213> Homo sapiens

<400> 429
 Arg Gln Thr Lys Val Asn Leu Lys Glu Thr Arg Ser Phe Glu Ile Ile
 1 5 10 15
 Val Trp Gly Phe Tyr Lys Ser Asn Tyr Cys His Leu His Pro Asp Ser
 20 25 30
 Phe Lys Leu Leu Ile His Pro
 35

<210> 430
 <211> 133
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (81)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (85)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 430
 Ala Arg Ala Pro Arg Val Pro Pro Ala Pro His Thr Pro Ser Lys Met
 1 5 10 15
 Gly Lys Glu Lys Thr His Ile Asn Ile Val Val Ile Gly His Val Asp
 20 25 30

375

Ser Gly Lys Ser Thr Thr Thr Gly His Leu Ile Tyr Lys Cys Gly Gly
 35 40 45
 Ile Asp Lys Arg Thr Ile Glu Lys Phe Glu Lys Glu Ala Ala Glu Met
 50 55 60
 Gly Lys Gly Ser Phe Lys Tyr Ala Trp Val Leu Asp Lys Leu Lys Ala
 65 70 75 80
 Xaa Val Ser Ala Xaa Ile Thr Ile Asp Ile Ser Leu Trp Lys Phe Glu
 85 90 95
 Thr Thr Lys Tyr Tyr Ile Thr Ile Ile Asp Ala Pro Gly His Arg Asp
 100 105 110
 Phe Ile Lys Asn Met Ile Thr Gly Thr Ser Gln Ala Asp Cys Ala Val
 115 120 125
 Leu Ile Val Ala Ala
 130

<210> 431
 <211> 190
 <212> PRT
 <213> Homo sapiens

<400> 431
 Leu Cys Trp Ala Arg Pro Leu Pro Ser Gly Pro Val Leu Leu Ala Ala
 1 5 10 15
 Asn Lys Asp Ser Ser Trp Cys Pro Thr Cys Leu Val His Cys Cys Val
 20 25 30
 Asn Pro Gly Gly Ser Gly His Arg Arg Gln Pro Arg Pro Arg Val Gln
 35 40 45
 Glu Lys Cys Ser Leu Glu Ala Arg Thr Thr Ala Ser His Trp Gly Arg
 50 55 60
 Arg Gly Pro Arg Thr Thr Ser Ala Ser Tyr Leu Pro Ala Ser Ala Arg
 65 70 75 80
 Gly Pro Arg Asp Ala Val Leu Phe Gln Pro Pro Ala Leu Gly Arg Gly
 85 90 95
 His Ala Ser Arg Ile Gln Gly Ala Gly Gly Leu Ser Thr Ala Arg Thr
 100 105 110

376

Cys Leu Leu Ala Ala Ala Val Gly Glu His Gly Gly Cys Gln Arg
 115 120 125

Leu Leu Trp Lys Val Ala Ala Ser Glu Met Ala Gly Ala Ala Gly Val
 130 135 140

Arg Leu His Thr Ala Gln Val Ser Ser Gly Arg Leu Ser Trp Gly Gly
 145 150 155 160

Ser Ser Ser Ala Glu Gly Trp Trp Gly Val Gln Ser Val Ile Leu Gly
 165 170 175

Ala Val Cys Pro Thr Pro Ala Trp Gly Pro His Phe Arg Arg
 180 185 190

<210> 432

<211> 310

<212> PRT

<213> Homo sapiens

<400> 432

Gly Pro His Gly Asn Gly Glu Val Arg Trp Pro Leu Pro Pro Pro Pro
 1 5 10 15

Pro Arg Phe Val Ala Arg Arg Lys Met Ala Asp Leu Glu Glu Gln Leu
 20 25 30

Ser Asp Glu Glu Lys Val Arg Ile Ala Ala Lys Phe Ile Ile His Ala
 35 40 45

Pro Pro Gly Glu Phe Asn Glu Val Phe Asn Asp Val Arg Leu Leu Leu
 50 55 60

Asn Asn Asp Asn Leu Leu Arg Glu Gly Ala Ala His Ala Phe Ala Gln
 65 70 75 80

Tyr Asn Leu Asp Gln Phe Thr Pro Val Lys Ile Glu Gly Tyr Glu Asp
 85 90 95

Gln Val Leu Ile Thr Glu His Gly Asp Leu Gly Asn Gly Lys Phe Leu
 100 105 110

Asp Pro Lys Asn Arg Ile Cys Phe Lys Phe Asp His Leu Arg Lys Glu
 115 120 125

Ala Thr Asp Pro Arg Pro Cys Glu Val Glu Asn Ala Val Glu Ser Trp
 130 135 140

Arg Thr Ser Val Glu Thr Ala Leu Arg Ala Tyr Val Lys Glu His Tyr

377

145 150 155 160
 Pro Asn Gly Val Cys Thr Val Tyr Gly Lys Lys Ile Asp Gly Gln Gln
 165 170 175
 Thr Ile Ile Ala Cys Ile Glu Ser His Gln Phe Gln Ala Lys Asn Phe
 180 185 190
 Trp Asn Gly Arg Trp Arg Ser Glu Trp Lys Phe Thr Ile Thr Pro Ser
 195 200 205
 Thr Thr Gln Val Val Gly Ile Leu Lys Ile Gln Val His Tyr Tyr Glu
 210 215 220
 Asp Gly Asn Val Gln Leu Val Ser His Lys Asp Ile Gln Asp Ser Leu
 225 230 235 240
 Thr Val Ser Asn Glu Val Gln Thr Ala Lys Glu Phe Ile Lys Ile Val
 245 250 255
 Glu Ala Ala Glu Asn Glu Tyr Gln Thr Ala Ile Ser Glu Asn Tyr Gln
 260 265 270
 Thr Met Ser Asp Thr Thr Phe Lys Ala Leu Arg Arg Gln Leu Pro Val
 275 280 285
 Thr Arg Thr Lys Ile Asp Trp Asn Lys Ile Leu Ser Tyr Lys Ile Gly
 290 295 300
 Lys Glu Met Gln Asn Ala
 305 310

<210> 433

<211> 289

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (287)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (288)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 433

Gln Ser Cys Thr Ser Gly Ser Ser Lys Pro Asn Ser Pro Ser Ile Ser

378

1	5	10	15
Pro Ser Ile Leu Ser Asn Thr Glu His Lys Arg Gly Pro Glu Val Thr	20	25	30
Ser Gln Gly Val Gln Thr Ser Ser Pro Ala Cys Lys Gln Glu Lys Asp	35	40	45
Asp Lys Glu Glu Lys Lys Asp Ala Ala Glu Gln Val Arg Lys Ser Thr	50	55	60
Leu Asn Pro Asn Ala Lys Glu Phe Asn Pro Arg Ser Phe Ser Gln Pro	65	70	75
Lys Pro Ser Thr Thr Pro Thr Ser Pro Arg Pro Gln Ala Gln Pro Ser	85	90	95
Pro Ser Met Val Gly His Gln Gln Pro Thr Pro Val Tyr Thr Gln Pro	100	105	110
Val Cys Phe Ala Pro Asn Met Met Tyr Pro Val Pro Val Ser Pro Gly	115	120	125
Val Gln Pro Leu Tyr Pro Ile Pro Met Thr Pro Met Pro Val Asn Gln	130	135	140
Ala Lys Thr Tyr Arg Ala Gly Lys Val Pro Asn Met Pro Gln Gln Arg	145	150	155
Gln Asp Gln His His Gln Ser Ala Met Met His Pro Ala Ser Ala Ala	165	170	175
Gly Pro Pro Ile Ala Ala Thr Pro Pro Ala Tyr Ser Thr Gln Tyr Val	180	185	190
Ala Tyr Ser Pro Gln Gln Phe Pro Asn Gln Pro Leu Val Gln His Val	195	200	205
Pro His Tyr Gln Ser Gln His Pro His Val Tyr Ser Pro Val Ile Gln	210	215	220
Gly Asn Ala Arg Met Met Ala Pro Pro Thr His Ala Gln Pro Gly Leu	225	230	235
Val Ser Ser Ser Ala Thr Gln Tyr Gly Ala His Glu Gln Thr His Ala	245	250	255
Met Tyr Ala Cys Pro Lys Leu Pro Tyr Asn Lys Glu Thr Ser Pro Ser	260	265	270
Phe Tyr Phe Ala Ile Ser Thr Gly Ser Leu Ala Gln Gln Tyr Xaa Xaa			

379

275

280

285

Pro

<210> 434

<211> 147

<212> PRT

<213> Homo sapiens

<400> 434

Lys Val Thr Pro Asp Leu Lys Pro Thr Glu Ala Ser Ser Ser Ala Phe
 1 5 10 15

Arg Leu Met Pro Ala Leu Gly Val Ser Val Ala Asp Gln Lys Gly Lys
 20 25 30

Ser Thr Val Ala Ser Ser Glu Ala Lys Pro Ala Ala Thr Ile Arg Ile
 35 40 45

Val Gln Gly Leu Gly Val Met Pro Pro Lys Ala Gly Gln Thr Ile Thr
 50 55 60

Val Ala Thr His Ala Lys Gln Gly Ala Ser Val Ala Ser Gly Ser Gly
 65 70 75 80

Thr Val His Thr Ser Ala Val Ser Leu Pro Ser Met Asn Ala Ala Val
 85 90 95

Ser Lys Thr Val Ala Val Ala Ser Gly Ala Ala Arg Pro Pro Ser Ala
 100 105 110

Ser Ala Gln Glu Pro Pro Pro Cys Gly Arg Ser Leu Ser Ala Pro Arg
 115 120 125

Leu Cys Pro Arg Pro Arg Leu Gly Ser Cys Leu His Gly Ser Gln Phe
 130 135 140

Pro Ser Leu
 145

<210> 435

<211> 151

<212> PRT

<213> Homo sapiens

<220>

380

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (15)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (79)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 435

Gly	Ser	Gly	Thr	Lys	Asp	Pro	Ser	Xaa	Cys	Asn	Thr	Gln	Thr	Xaa	Ala
1				5				10						15	

His	Thr	His	Thr	Gly	Gly	Glu	Ile	Ser	Leu	Phe	Ser	Met	Ser	Phe	Phe
			20					25					30		

Ser	Trp	Ala	Glu	Thr	Gly	Tyr	Cys	Pro	Gly	Gln	Leu	Pro	Glu	Lys	His
		35					40					45			

Arg	Arg	Glu	Leu	Arg	Ser	Ala	Arg	Pro	Ser	Ser	Leu	Ala	Pro	Gly	Phe
		50				55					60				

Gly	Gly	Pro	Arg	Thr	Ala	Asp	Arg	Gly	Trp	Ser	Trp	Arg	Leu	Xaa	Ser
	65				70				75					80	

Arg	Ala	Tyr	Thr	Trp	Arg	Asn	Ala	Pro	Pro	Ser	Ser	Pro	Ser	Leu	Gln
				85				90						95	

Thr	Trp	Gly	Trp	Leu	Gly	Pro	Glu	Gly	Cys	Asp	Glu	Glu	Lys	Arg	Ala
		100					105						110		

Ser	Val	Gly	Met	Arg	Gln	Glu	Gly	Ile	Asp	Phe	Asp	Cys	Asp	Leu	Trp
		115				120					125				

Gly	Phe	Leu	Pro	Ala	Leu	Asp	Asn	Pro	Ala	Lys	Asp	Cys	Phe	Phe	Leu
	130					135					140				

Ser	Leu	Ala	Arg	Arg	Gly	Pro
145					150	

<210> 436

<211> 180

<212> PRT

<213> Homo sapiens

381

<220>

<221> SITE

<222> (42)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (123)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 436

Ala Pro Ala Ser Pro Val Met Pro Pro Gln Thr Gln Ser Pro Gly Gln
 1 5 10 15

Pro Ala Gln Pro Ala Pro Met Val Pro Leu His Gln Lys Gln Ser Arg
 20 25 30

Ile Thr Pro Ile Gln Lys Pro Arg Gly Xaa Asp Pro Val Glu Ile Leu
 35 40 45

Gln Glu Arg Glu Tyr Arg Leu Gln Ala Arg Ile Ala His Arg Ile Gln
 50 55 60

Glu Leu Glu Asn Leu Pro Gly Ser Leu Ala Gly Asp Leu Arg Thr Lys
 65 70 75 80

Ala Thr Ile Glu Leu Lys Ala Leu Arg Leu Leu Asn Phe Gln Arg Gln
 85 90 95

Leu Arg Gln Glu Val Val Val Cys Met Arg Arg Asp Thr Ala Leu Glu
 100 105 110

Thr Ala Leu Asn Ala Lys Ala Tyr Lys Arg Xaa Ser Ala Ser Pro Cys
 115 120 125

Ala Arg Pro Ala Ser Leu Arg Ser Trp Arg Ser Ser Arg Arg Ser Ser
 130 135 140

Arg Ser Ala Ser Ala Gly Arg Ser Thr Arg Asn Thr Ser Ile Ala Phe
 145 150 155 160

Ser Ser Met Pro Arg Ile Ser Arg Asn Ile Thr Asp Pro Ser Gln Ala
 165 170 175

Lys Ser Arg Ser
 180

<210> 437

382

<211> 415
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (8)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (94)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (96)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (170)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 437
 Arg Lys Tyr Leu Val Pro Leu Xaa Lys Lys Leu Tyr Leu Lys Trp Ala
 1 5 10 15
 Leu Glu Glu Tyr Leu Asp Glu Phe Asp Pro Cys His Cys Arg Pro Cys
 20 25 30
 Gln Asn Gly Gly Leu Ala Thr Val Glu Gly Thr His Cys Leu Cys His
 35 40 45
 Cys Lys Pro Tyr Thr Phe Gly Ala Ala Cys Glu Gln Gly Val Leu Val
 50 55 60
 Gly Asn Gln Ala Gly Gly Val Asp Gly Gly Trp Ser Cys Trp Ser Ser
 65 70 75 80
 Trp Ser Pro Cys Val Gln Gly Lys Lys Thr Arg Ser Arg Xaa Cys Xaa
 85 90 95
 Asn Pro Pro Pro Ser Gly Gly Gly Arg Ser Cys Val Gly Glu Thr Thr
 100 105 110
 Glu Ser Thr Gln Cys Glu Asp Glu Glu Leu Glu His Leu Arg Leu Leu
 115 120 125
 Glu Pro His Cys Phe Pro Leu Ser Leu Val Pro Thr Glu Phe Cys Pro
 130 135 140

383

Ser Pro Pro Ala Leu Lys Asp Gly Phe Val Gln Asp Glu Gly Thr Met
 145 150 155 160
 Phe Pro Val Gly Lys Asn Val Val Tyr Xaa Cys Asn Glu Gly Tyr Ser
 165 170 175
 Leu Ile Gly Asn Pro Val Ala Arg Cys Gly Glu Asp Leu Arg Trp Leu
 180 185 190
 Val Gly Glu Met His Cys Gln Lys Ile Ala Cys Val Leu Pro Val Leu
 195 200 205
 Met Asp Gly Ile Gln Ser His Pro Gln Lys Pro Phe Tyr Thr Val Gly
 210 215 220
 Glu Lys Val Thr Val Ser Cys Ser Gly Gly Met Ser Leu Glu Gly Pro
 225 230 235 240
 Ser Ala Phe Leu Cys Gly Ser Ser Leu Lys Trp Ser Pro Glu Met Lys
 245 250 255
 Asn Ala Arg Cys Val Gln Lys Glu Asn Pro Leu Thr Gln Ala Val Pro
 260 265 270
 Lys Cys Gln Arg Trp Glu Lys Leu Gln Asn Ser Arg Cys Val Cys Lys
 275 280 285
 Met Pro Tyr Glu Cys Gly Pro Ser Leu Asp Val Cys Ala Gln Asp Glu
 290 295 300
 Arg Ser Lys Arg Ile Leu Pro Leu Thr Val Cys Lys Met His Val Leu
 305 310 315 320
 His Cys Gln Gly Arg Asn Tyr Thr Leu Thr Gly Arg Asp Ser Cys Thr
 325 330 335
 Leu Pro Ala Ser Ala Glu Lys Ala Cys Gly Ala Cys Pro Leu Trp Gly
 340 345 350
 Lys Cys Asp Ala Glu Ser Ser Lys Cys Val Cys Arg Glu Ala Ser Glu
 355 360 365
 Cys Glu Glu Glu Gly Phe Ser Ile Cys Val Glu Val Asn Gly Lys Glu
 370 375 380
 Gln Thr Met Ser Glu Cys Glu Ala Gly Ala Leu Arg Cys Arg Gly Gln
 385 390 395 400
 Ser Ile Ser Val Thr Ser Ile Arg Pro Cys Ala Ala Glu Thr Gln
 405 410 415

<210> 438
 <211> 285
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (16)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (17)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (18)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 438
 Leu Ile Arg Leu Thr Ile Gly Lys Ala Gly Ser Leu Gln Tyr Arg Xaa
 1 5 10 15

 Xaa Xaa Phe Pro Gly Met Glu Ala Phe Leu Gly Ser Arg Ser Gly Leu
 20 25 30

 Trp Ala Gly Gly Pro Ala Pro Gly Gln Phe Tyr Arg Ile Pro Ser Thr
 35 40 45

 Pro Asp Ser Phe Met Asp Pro Ala Ser Ala Leu Tyr Arg Gly Pro Ile
 50 55 60

 Thr Arg Thr Gln Asn Pro Met Val Thr Gly Thr Ser Val Leu Gly Val
 65 70 75 80

 Lys Phe Glu Gly Gly Val Val Ile Ala Ala Asp Met Leu Gly Ser Tyr
 85 90 95

 Gly Ser Leu Ala Arg Phe Arg Asn Ile Ser Arg Ile Met Arg Val Asn
 100 105 110

 Asn Ser Thr Met Leu Gly Ala Ser Gly Asp Tyr Ala Asp Phe Gln Tyr
 115 120 125

 Leu Lys Gln Val Leu Gly Gln Met Val Ile Asp Glu Glu Leu Leu Gly
 130 135 140

385

Asp Gly His Ser Tyr Ser Pro Arg Ala Ile His Ser Trp Leu Thr Arg
 145 150 155 160

Ala Met Tyr Ser Arg Arg Ser Lys Met Asn Pro Leu Trp Asn Thr Met
 165 170 175

Val Ile Gly Gly Tyr Ala Asp Gly Glu Ser Phe Leu Gly Tyr Val Asp
 180 185 190

Met Leu Gly Val Ala Tyr Glu Ala Pro Ser Leu Ala Thr Gly Tyr Gly
 195 200 205

Ala Tyr Leu Ala Gln Pro Leu Leu Arg Glu Val Leu Glu Lys Gln Pro
 210 215 220

Val Leu Ser Gln Thr Glu Ala Arg Asp Leu Val Glu Arg Cys Met Arg
 225 230 235 240

Val Leu Tyr Tyr Arg Asp Ala Arg Ser Tyr Asn Arg Phe Gln Ile Ala
 245 250 255

Thr Val Thr Glu Lys Gly Val Glu Ile Glu Gly Pro Leu Ser Thr Glu
 260 265 270

Thr Asn Trp Asp Ile Ala His Met Ile Ser Gly Phe Glu
 275 280 285

<210> 439

<211> 185

<212> PRT

<213> Homo sapiens

<400> 439

Asn Ser Ala Ala His Lys Lys Gly Lys Leu Pro Ile Val Asn Glu Asp
 1 5 10 15

Asp Glu Leu Val Ala Ile Ile Ala Arg Thr Asp Leu Lys Lys Asn Arg
 20 25 30

Asp Tyr Pro Leu Ala Ser Lys Asp Ala Lys Lys Gln Leu Leu Cys Gly
 35 40 45

Ala Ala Ile Gly Thr His Glu Asp Asp Lys Tyr Arg Leu Asp Leu Leu
 50 55 60

Ala Gln Ala Gly Val Asp Val Val Val Leu Asp Ser Ser Gln Gly Asn
 65 70 75 80

Ser Ile Phe Gln Ile Asn Met Ile Lys Tyr Ile Lys Asp Lys Tyr Pro

386

	85		90		95
Asn Leu Gln Val Ile Gly Gly Asn Val Val Thr Ala Ala Gln Ala Lys					
	100		105		110
Asn Leu Ile Asp Ala Gly Val Asp Ala Leu Arg Val Gly Met Gly Ser					
	115		120		125
Gly Ser Ile Cys Ile Thr Gln Glu Val Leu Ala Cys Gly Arg Pro Gln					
	130		135		140
Ala Thr Ala Val Tyr Lys Val Ser Glu Tyr Ala Arg Arg Phe Gly Val					
	145		150		155
Pro Val Ile Ala Asp Gly Gly Ile Gln Asn Val Gly His Ile Ala Lys					
	165		170		175
Ala Leu Ala Leu Gly Ala Pro Gln Ser					
	180		185		

<210> 440

<211> 211

<212> PRT

<213> Homo sapiens

<400> 440

Leu Gln Gly Arg Ser Thr Pro Ile Trp Pro Ala Leu Ala Thr Val Thr					
1		5		10	15
Ser Arg Thr Pro Ala Leu Gly Pro Gln Ala Gly Ile Asp Thr Asn Glu					
	20		25		30
Ile Ala Pro Leu Glu Pro Asp Ala Pro Pro Asp Ala Cys Glu Ala Ser					
	35		40		45
Phe Asp Ala Val Ser Thr Ile Arg Gly Glu Leu Phe Phe Phe Lys Ala					
	50		55		60
Gly Phe Val Trp Arg Leu Arg Gly Gly Gln Leu Gln Pro Gly Tyr Pro					
	65		70		75
Ala Leu Ala Ser Arg His Trp Gln Gly Leu Pro Ser Pro Val Asp Ala					
	85		90		95
Ala Phe Glu Asp Ala Gln Gly His Ile Trp Phe Phe Gln Gly Ala Gln					
	100		105		110
Tyr Trp Val Tyr Asp Gly Glu Lys Pro Val Leu Gly Pro Ala Pro Leu					
	115		120		125

387

Thr Glu Leu Gly Leu Val Arg Phe Pro Val His Ala Ala Leu Val Trp
 130 135 140

Gly Pro Glu Lys Asn Lys Ile Tyr Phe Phe Arg Gly Arg Asp Tyr Trp
 145 150 155 160

Arg Phe His Pro Ser Thr Arg Arg Val Asp Ser Pro Val Pro Arg Arg
 165 170 175

Pro Leu Thr Gly Glu Gly Cys Pro Leu Arg Ser Thr Leu Pro Ser Arg
 180 185 190

Met Leu Met Ala Met Pro Thr Ser Cys Ala Ala Ala Ser Thr Gly Ser
 195 200 205

Leu Thr Leu
 210

<210> 441

<211> 80

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (40)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 441

Gly Gly Ala Gly Lys Leu Leu Ser Phe Thr His Ser Ala Pro Trp Ser
 1 5 10 15

Arg Leu Trp Ser Ser Leu Gly Lys Arg Val Thr Gly Glu Ser Gln Gly
 20 25 30

Leu Glu Lys Leu Pro Gly Thr Xaa Asp Gly Leu Ala Ala Leu Thr Gln
 35 40 45

Asp Pro Leu Pro Leu Pro Pro Pro Leu Cys Arg Asn Thr Gly Thr Pro
 50 55 60

Arg Gly Lys Met Ser Phe Ser Arg Leu Gln Phe Ser Pro Arg Lys Leu
 65 70 75 80

388

<210> 442
<211> 567
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (205)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (212)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (469)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (503)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (505)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (517)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (535)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (546)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 442
Asn Val His Leu Tyr Ile Met Tyr Tyr Met Glu Ala Lys His Ala Val
1 5 10 15

Ser Phe Met Thr Cys Thr Gln Asn Val Ala Pro Asp Met Phe Arg Thr

389

20	25	30
Ile Pro Pro Glu Ala Asn Ile Pro Ile Pro Val Lys Ser Asp Met Val		
35	40	45
Met Met His Glu His His Lys Glu Thr Glu Tyr Lys Asp Lys Ile Pro		
50	55	60
Leu Leu Gln Gln Pro Lys Arg Glu Glu Glu Glu Val Leu Asp Gln Gly		
65	70	75
Asp Phe Tyr Ser Leu Leu Ser Lys Leu Leu Gly Glu Arg Glu Asp Val		
85	90	95
Val His Val His Lys Tyr Asn Pro Thr Glu Lys Ala Glu Ser Glu Ser		
100	105	110
Asp Leu Val Ala Glu Ile Ala Asn Val Val Gln Lys Lys Asp Leu Gly		
115	120	125
Arg Ser Asp Ala Arg Glu Gly Ala Glu His Glu Arg Gly Asn Ala Ile		
130	135	140
Leu Val Arg Asp Arg Ile His Lys Phe His Arg Leu Val Ser Thr Leu		
145	150	155
Arg Pro Pro Glu Ser Arg Val Phe Ser Leu Gln Gln Pro Pro Pro Gly		
165	170	175
Glu Gly Thr Trp Glu Pro Glu His Thr Gly Asp Phe His Met Glu Glu		
180	185	190
Ala Leu Asp Trp Pro Gly Val Tyr Leu Leu Pro Gly Xaa Val Ser Gly		
195	200	205
Val Ala Leu Xaa Pro Lys Asn Asn Leu Val Ile Phe His Arg Gly Asp		
210	215	220
His Val Trp Asp Gly Asn Ser Phe Asp Ser Lys Phe Val Tyr Gln Gln		
225	230	235
Ile Gly Leu Gly Pro Ile Glu Glu Asp Thr Ile Leu Val Ile Asp Pro		
245	250	255
Asn Asn Ala Ala Val Leu Gln Ser Ser Gly Lys Asn Leu Phe Tyr Leu		
260	265	270
Pro His Gly Leu Ser Ile Asp Lys Asp Gly Asn Tyr Trp Val Thr Asp		
275	280	285
Val Ala Leu His Gln Val Phe Lys Leu Asp Pro Asn Asn Lys Glu Gly		

390

290	295	300
Pro Val Leu Ile Leu Gly Arg Ser Met Gln Pro Gly Ser Asp Gln Asn		
305	310	315 320
His Phe Cys Gln Pro Thr Asp Val Ala Val Asp Pro Gly Thr Gly Ala		
	325	330 335
Ile Tyr Val Ser Asp Gly Tyr Cys Asn Ser Arg Ile Val Gln Phe Ser		
	340	345 350
Pro Ser Gly Lys Phe Ile Thr Gln Trp Gly Glu Glu Ser Ser Gly Ser		
	355	360 365
Ser Pro Leu Pro Gly Gln Phe Thr Val Pro His Ser Leu Ala Leu Val		
	370	375 380
Pro Leu Leu Gly Gln Leu Cys Val Ala Asp Arg Glu Asn Gly Arg Ile		
385	390	395 400
Gln Cys Phe Lys Thr Asp Thr Lys Glu Phe Val Arg Glu Ile Lys His		
	405	410 415
Ser Ser Phe Gly Arg Asn Val Phe Ala Ile Ser Tyr Ile Pro Gly Leu		
	420	425 430
Leu Phe Ala Val Asn Gly Lys Pro His Phe Gly Asp Gln Glu Pro Val		
	435	440 445
Gln Gly Phe Val Met Asn Phe Ser Asn Gly Glu Ile Ile Asp Ile Phe		
	450	455 460
Lys Pro Val Arg Xaa Leu Leu Asp Met Pro His Asp Ile Val Ala Ser		
465	470	475 480
Glu Asp Gly Thr Val Tyr Ile Gly Arg Cys Ser Tyr Gln His Arg Val		
	485	490 495
Gly Ser Ser Thr Leu Asp Xaa Arg Xaa Leu Gly Thr Ser Val Gln Phe		
	500	505 510
Lys Lys Gly Leu Xaa Ile Glu Val Gln Gly Asn Pro Lys Lys Pro Glu		
	515	520 525
Gly Ile Cys Cys Phe Pro Xaa Thr Thr Leu Arg Val Ile Pro Val Val		
	530	535 540
Gly Xaa Trp Arg Gly His Gly Pro Asn Leu Ile Pro Val Gly Lys Asn		
545	550	555 560
Pro Arg Gly Pro Leu Gly Arg		

391

565

<210> 443
 <211> 129
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (123)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (127)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (129)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 443
 Arg Pro Ser Cys Ser Pro Gly Ser Val Ser Ala Ala Ala Val Asn Met
 1 5 10 15

Glu Pro Pro Asp Ala Pro Ala Gln Ala Arg Gly Ala Pro Arg Leu Leu
 20 25 30

Leu Leu Ala Val Leu Leu Ala Ala His Pro Asp Ala Gln Ala Glu Val
 35 40 45

Arg Leu Ser Val Pro Pro Leu Val Glu Val Met Arg Gly Lys Ser Val
 50 55 60

Ile Leu Asp Cys Thr Pro Thr Gly Thr His Asp His Tyr Met Leu Glu
 65 70 75 80

Trp Phe Leu Thr Asp Arg Ser Gly Ala Arg Pro Arg Leu Ala Ser Ala
 85 90 95

Glu Met Gln Gly Ser Glu Leu Gln Val Thr Met His Asp Thr Arg Gly
 100 105 110

Arg Ser Pro Tyr Gln Leu Gly Leu Pro Xaa Gly Ala Trp Xaa Leu
 115 120 125

Xaa

392

<210> 444

<211> 131

<212> PRT

<213> Homo sapiens

<400> 444

Glu Pro Arg Val Glu Arg Glu Thr Pro Gly Gln Pro Phe Ser Ser Ser
 1 5 10 15

Phe Pro Ser Pro Ser Pro Phe Pro Asn Val Ala Ser Met Trp Val Leu
 20 25 30

Gly Thr Trp Glu Lys Pro Leu Leu Cys His Phe Phe Ser Leu Phe Pro
 35 40 45

Ser Ser Pro Pro Thr Val Trp Leu Met Met Ser Ser Gly Val Met Val
 50 55 60

Thr Thr Pro Cys Ser Leu Phe Trp Tyr Phe Pro Cys Gln Phe Pro Leu
 65 70 75 80

Ser Ala Arg Leu Cys Pro Lys Ile Pro Ser Ala Ser Ser Leu His Val
 85 90 95

Ala Glu Gly Pro Gly Leu Pro Gln Val Pro Cys Leu Ser Asn Lys Val
 100 105 110

Glu Thr Ile Lys Pro Gly Lys Lys Lys Gly Gly Arg Ser Lys Gly
 115 120 125

Ser Pro Arg
 130

<210> 445

<211> 405

<212> PRT

<213> Homo sapiens

<400> 445

Gly Thr Gly Leu Val Pro Ile Arg Gln Ser Thr Lys Phe Asp Ser Ser
 1 5 10 15

Leu Asp Arg Lys Asp Lys Phe Ser Phe Asp Leu Gly Lys Gly Glu Val
 20 25 30

Ile Lys Ala Trp Asp Ile Ala Ile Ala Thr Met Lys Val Gly Glu Val

393

35	40	45
Cys His Ile Thr Cys Lys Pro Glu Tyr Ala Tyr Gly Ser Ala Gly Ser		
50	55	60
Pro Pro Lys Ile Pro Pro Asn Ala Thr Leu Val Phe Glu Val Glu Leu		
65	70	75 80
Phe Glu Phe Lys Gly Glu Asp Leu Thr Glu Glu Glu Asp Gly Gly Ile		
	85	90 95
Ile Arg Arg Ile Gln Thr Arg Gly Glu Gly Tyr Ala Lys Pro Asn Glu		
	100	105 110
Gly Ala Ile Val Glu Val Ala Leu Glu Gly Tyr Tyr Lys Asp Lys Leu		
	115	120 125
Phe Asp Gln Arg Glu Leu Arg Phe Glu Ile Gly Glu Gly Glu Asn Leu		
	130	135 140
Asp Leu Pro Tyr Gly Leu Glu Arg Ala Ile Gln Arg Met Glu Lys Gly		
145	150	155 160
Glu His Ser Ile Val Tyr Leu Lys Pro Ser Tyr Ala Phe Gly Ser Val		
	165	170 175
Gly Lys Glu Lys Phe Gln Ile Pro Pro Asn Ala Glu Leu Lys Tyr Glu		
	180	185 190
Leu His Leu Lys Ser Phe Glu Lys Ala Lys Glu Ser Trp Glu Met Asn		
	195	200 205
Ser Glu Glu Lys Leu Glu Gln Ser Thr Ile Val Lys Glu Arg Gly Thr		
	210	215 220
Val Tyr Phe Lys Glu Gly Lys Tyr Lys Gln Ala Leu Leu Gln Tyr Lys		
225	230	235 240
Lys Ile Val Ser Trp Leu Glu Tyr Glu Ser Ser Phe Ser Asn Glu Glu		
	245	250 255
Ala Gln Lys Ala Gln Ala Leu Arg Leu Ala Ser His Leu Asn Leu Ala		
	260	265 270
Met Cys His Leu Lys Leu Gln Ala Phe Ser Ala Ala Ile Glu Ser Cys		
	275	280 285
Asn Lys Ala Leu Glu Leu Asp Ser Asn Asn Glu Lys Gly Leu Phe Arg		
	290	295 300
Arg Gly Glu Ala His Leu Ala Val Asn Asp Phe Glu Leu Ala Arg Ala		

394

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305              310              315              320
Asp Phe Gln Lys Val Leu Gln Leu Tyr Pro Asn Asn Lys Ala Ala Lys
      325              330              335

Thr Gln Leu Ala Val Cys Gln Gln Arg Ile Arg Arg Gln Leu Ala Arg
      340              345              350

Glu Lys Lys Leu Tyr Ala Asn Met Phe Glu Arg Leu Ala Glu Glu Glu
      355              360              365

Asn Lys Ala Lys Ala Glu Ala Ser Ser Gly Asp His Pro Thr Asp Thr
      370              375              380

Glu Met Lys Glu Glu Gln Lys Ser Asn Thr Ala Gly Ser Gln Ser Gln
385              390              395              400

Val Glu Thr Glu Ala
      405

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<210> 446
 <211> 232
 <212> PRT
 <213> Homo sapiens

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<400> 446
Pro Leu Val Pro Ser Ser Gln Lys Ala Leu Leu Leu Glu Leu Lys Gly
  1              5              10              15

Leu Gln Glu Glu Pro Val Glu Gly Phe Arg Val Thr Leu Val Asp Glu
      20              25              30

Gly Asp Leu Tyr Asn Trp Glu Val Ala Ile Phe Gly Pro Pro Asn Thr
      35              40              45

Tyr Tyr Glu Gly Gly Tyr Phe Lys Ala Arg Leu Lys Phe Pro Ile Asp
      50              55              60

Tyr Pro Tyr Ser Pro Pro Ala Phe Arg Phe Leu Thr Lys Met Trp His
      65              70              75              80

Pro Asn Ile Tyr Glu Thr Gly Asp Val Cys Ile Ser Ile Leu His Pro
      85              90              95

Pro Val Asp Asp Pro Gln Ser Gly Glu Leu Pro Ser Glu Arg Trp Asn
      100             105             110

Pro Thr Gln Asn Val Arg Thr Ile Leu Leu Ser Val Ile Ser Leu Leu
      115             120             125

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395

Asn Glu Pro Asn Thr Phe Ser Pro Ala Asn Val Asp Ala Ser Val Met
 130 135 140
 Tyr Arg Lys Trp Lys Glu Ser Lys Gly Lys Asp Arg Glu Tyr Thr Asp
 145 150 155 160
 Ile Ile Arg Lys Gln Val Leu Gly Thr Arg Trp Thr Arg Val Asn Gly
 165 170 175
 Val Lys Val Pro Thr Thr Leu Ala Glu Tyr Cys Val Lys Thr Lys Ala
 180 185 190
 Pro Ala Pro Asp Glu Gly Ser Asp Leu Phe Tyr Asp Asp Tyr Tyr Glu
 195 200 205
 Asp Gly Glu Val Glu Glu Glu Ala Asp Ser Cys Phe Gly Asp Asp Glu
 210 215 220
 Asp Asp Ser Gly Thr Glu Glu Ser
 225 230

<210> 447

<211> 356

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (12)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (53)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (191)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (263)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 447

Cys Ser Pro Pro Pro Pro Pro Ala Ala Ala Ala Xaa Ala Ala Ala Ala

396

1	5	10	15
Ala Met Ala Gln Tyr Lys Gly Ala Ala Ser Glu Ala Gly Arg Ala Met	20	25	30
His Leu Met Lys Lys Arg Glu Lys Gln Arg Glu Gln Met Glu Gln Met	35	40	45
Lys Gln Arg Ile Xaa Glu Glu Asn Ile Met Lys Ser Asn Ile Asp Lys	50	55	60
Lys Phe Ser Ala His Tyr Asp Ala Val Glu Ala Glu Leu Lys Ser Ser	65	70	75
Thr Val Gly Leu Val Thr Leu Asn Asp Met Lys Ala Lys Gln Glu Ala	85	90	95
Leu Val Lys Glu Arg Glu Lys Gln Leu Ala Lys Lys Glu Gln Ser Lys	100	105	110
Glu Leu Gln Met Lys Leu Glu Lys Leu Arg Glu Lys Glu Arg Lys Lys	115	120	125
Glu Ala Lys Arg Lys Ile Ser Ser Leu Ser Phe Thr Leu Glu Glu Glu	130	135	140
Glu Glu Gly Gly Glu Glu Glu Glu Glu Ala Ala Met Tyr Glu Glu Glu	145	150	155
Met Glu Arg Glu Glu Ile Thr Thr Lys Lys Arg Lys Leu Gly Lys Asn	165	170	175
Pro Asp Val Asp Thr Ser Phe Leu Pro Asp Arg Asp Arg Glu Xaa Glu	180	185	190
Glu Asn Arg Leu Arg Glu Glu Leu Arg Gln Glu Trp Glu Ala Lys Gln	195	200	205
Glu Lys Ile Lys Ser Glu Glu Ile Glu Ile Thr Phe Ser Tyr Trp Asp	210	215	220
Gly Ser Gly His Arg Arg Thr Val Lys Met Arg Lys Gly Asn Thr Met	225	230	235
Gln Gln Phe Leu Gln Lys Ala Leu Glu Ile Leu Arg Lys Asp Phe Ser	245	250	255
Glu Leu Arg Ser Ala Gly Xaa Glu Gln Leu Met Tyr Ile Lys Glu Asp	260	265	270
Leu Ile Ile Pro His His His Ser Phe Tyr Asp Phe Ile Val Thr Lys			

397

275 280 285
 Ala Arg Gly Lys Ser Gly Pro Leu Phe Asn Phe Asp Val His Asp Asp
 290 295 300
 Val Arg Leu Leu Ser Asp Ala Thr Val Glu Lys Asp Glu Ser His Ala
 305 310 315 320
 Gly Lys Val Val Leu Arg Ser Trp Tyr Glu Lys Asn Lys His Ile Phe
 325 330 335
 Pro Ala Ser Arg Trp Glu Pro Tyr Asp Pro Glu Lys Lys Trp Asp Lys
 340 345 350
 Tyr Thr Ile Arg
 355

<210> 448
 <211> 88
 <212> PRT
 <213> Homo sapiens

<400> 448
 Lys Thr His Lys Met Cys Asp Ala Phe Val Gly Thr Trp Lys Leu Val
 1 5 10 15
 Ser Ser Glu Asn Phe Asp Asp Tyr Met Lys Glu Val Gly Val Gly Phe
 20 25 30
 Ala Thr Arg Lys Val Ala Gly Met Ala Lys Pro Asn Met Ile Ile Ser
 35 40 45
 Val Asn Gly Asp Val Ile Thr Ile Lys Ser Glu Ser Thr Phe Lys Asn
 50 55 60
 Thr Glu Ile Ser Phe Ile Leu Gly Gln Glu Phe Asp Glu Ala Leu Gln
 65 70 75 80
 Met Thr Gly Lys Ser Arg Ala Pro
 85

<210> 449
 <211> 171
 <212> PRT
 <213> Homo sapiens

<220>

398

<221> SITE

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (132)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 449

Leu Ile Leu Val Leu Met Phe Val Val Trp Met Lys Arg Arg Asp Lys
 1 5 10 15

Glu Arg Gln Ala Lys Gln Leu Leu Ile Asp Pro Glu Asp Asp Val Arg
 20 25 30

Asp Asn Ile Leu Lys Tyr Asp Glu Glu Gly Gly Gly Glu Glu Asp Gln
 35 40 45

Asp Tyr Asp Leu Ser Gln Leu Gln Gln Pro Asp Thr Val Glu Pro Asp
 50 55 60

Ala Ile Lys Pro Val Gly Ile Xaa Arg Met Asp Glu Arg Pro Ile His
 65 70 75 80

Ala Glu Pro Gln Tyr Pro Val Arg Ser Ala Ala Pro His Pro Gly Asp
 85 90 95

Ile Gly Asp Phe Ile Asn Glu Gly Leu Lys Ala Ala Asp Asn Asp Pro
 100 105 110

Thr Ala Pro Pro Tyr Asp Ser Leu Leu Val Phe Asp Tyr Glu Gly Ser
 115 120 125

Gly Ser Thr Xaa Gly Ser Leu Ser Ser Leu Asn Ser Ser Ser Ser Gly
 130 135 140

Gly Glu Gln Asp Tyr Asp Tyr Leu Asn Asp Trp Gly Pro Arg Phe Lys
 145 150 155 160

Lys Leu Ala Asp Met Tyr Gly Gly Gly Asp Asp
 165 170

<210> 450

<211> 34

<212> PRT

<213> Homo sapiens

<400> 450

399

Lys Val Lys Ala Cys Cys Lys Asp Ile Phe Phe Leu Leu Leu Glu Gly
 1 5 10 15
 Asn Thr Lys Arg Lys Ile Ser Phe Phe His Gly Ala Phe Asp Asn Phe
 20 25 30
 Ser Leu

<210> 451
 <211> 148
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (43)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (89)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 451
 Arg Thr Leu His Pro Ala Thr Gly Pro Arg Ala Arg Pro Pro Arg Gly
 1 5 10 15
 Trp Arg Arg Arg Leu Cys Ala Gln Gly Pro Ala Pro Asp Trp Asp Pro
 20 25 30
 Gly Val Pro Pro Gly Leu Ala Ser Cys Gly Xaa Thr Val Trp Leu His
 35 40 45
 Phe Ser Asp Pro Ser Leu Gly Arg Lys Val Lys Glu Thr Gly Pro Ala
 50 55 60
 Ser Ala Phe Gly Leu Trp Phe Leu Asp Arg Val Leu Ser Pro Ser Pro
 65 70 75 80
 Pro Ser Ser Pro Asn Leu Ser His Xaa Arg Pro Leu Pro Ala Ala Pro
 85 90 95
 Ser Leu Leu Gly Ile Gly Ser Pro Glu Pro Pro Ser Pro Glu Pro Pro
 100 105 110
 Thr Pro Leu Pro Gly Pro Cys Gly Cys Trp Ala Ser His Leu Lys Glu
 115 120 125

400

Gly Lys Val Val Gln Pro Glu Pro Val Glu Gln Cys Pro Val Trp Pro
130 135 140

Pro Lys Pro Lys
145

<210> 452
<211> 83
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (19)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (64)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (77)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (79)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 452
Asp Ser His Arg Pro Arg Ala Met Arg Ala Leu Trp Val Leu Gly Leu
1 5 10 15

Ser Cys Xaa Leu Leu Thr Phe Gly Ser Val Arg Xaa Asp Asp Glu Val
20 25 30

Asp Val Asp Gly Thr Val Glu Glu Asp Leu Gly Lys Ser Arg Glu Gly
35 40 45

Ser Arg Thr Asp Asp Glu Val Val Gln Arg Glu Glu Glu Ala Ile Xaa
50 55 60

401

Val Gly Trp Ile Lys Cys Ile Pro Asn Lys Arg Thr Xaa Glu Xaa Lys
 65 70 75 80

Ser Arg Lys

<210> 453

<211> 240

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (234)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 453

Gly Trp Leu Pro Cys Gly Ser Ser Val Val Pro Ala Thr Pro Gly Ser
 1 5 10 15

Pro Pro Ser Arg Phe Trp Leu Leu Pro Ala Met Ala Leu Arg Val Leu
 20 25 30

Leu Leu Thr Ala Leu Thr Leu Cys His Gly Phe Asn Leu Asp Thr Glu
 35 40 45

Asn Ala Met Thr Phe Gln Glu Asn Ala Arg Gly Phe Gly Gln Ser Val
 50 55 60

Val Gln Leu Gln Gly Ser Arg Val Val Val Gly Ala Pro Gln Glu Ile
 65 70 75 80

Val Ala Ala Asn Gln Arg Gly Ser Leu Tyr Gln Cys Asp Tyr Ser Thr
 85 90 95

Gly Ser Cys Glu Pro Ile His Leu Gln Val Pro Val Glu Ala Val Asn
 100 105 110

Met Ser Leu Gly Leu Ser Leu Ala Ala Thr Thr Ser Pro Pro Gln Leu
 115 120 125

Leu Ala Cys Gly Pro Thr Val His Gln Thr Cys Ser Glu Asn Thr Tyr
 130 135 140

Val Lys Gly Leu Cys Phe Leu Phe Gly Ser Asn Leu Arg Gln Gln Pro
 145 150 155 160

Gln Lys Phe Pro Glu Ala Leu Arg Gly Cys Pro Gln Glu Asp Ser Asp
 165 170 175

402

Ile Ala Phe Leu Ile Asp Gly Ser Gly Ser Ile Ile Pro His Asp Phe
 180 185 190

Arg Arg Met Lys Glu Phe Val Ser Thr Val Met Glu Gln Leu Lys Lys
 195 200 205

Ser Lys Thr Leu Phe Ser Leu Met Gln Tyr Ser Glu Glu Phe Arg Ile
 210 215 220

His Phe Thr Ser Lys Ser Ser Arg Thr Xaa Leu Thr Gln Asp His Trp
 225 230 235 240

<210> 454

<211> 244

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (206)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (227)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (229)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (239)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 454

Lys Trp Cys Ser Trp Thr Leu Leu Lys Ile Trp Glu Val Thr Cys Thr
 1 5 10 15

Trp Lys Leu Pro Thr Leu Ala Lys Phe Ser Pro Tyr Leu Gly Gln Met
 20 25 30

Ile Asn Leu Arg Arg Leu Leu Leu Ser His Ile His Ala Ser Ser Tyr

403

35 40 45
 Ile Ser Pro Glu Lys Glu Glu Gln Tyr Ile Ala Gln Phe Thr Ser Gln
 50 55 60
 Phe Leu Ser Leu Gln Cys Leu Gln Leu Leu Tyr Val Asp Ser Leu Phe
 65 70 75 80
 Phe Leu Arg Gly Arg Leu Asp Gln Leu Leu Arg His Val Met Asn Pro
 85 90 95
 Leu Glu Thr Leu Ser Ile Thr Asn Cys Arg Leu Ser Glu Gly Asp Val
 100 105 110
 Met His Leu Ser Gln Ser Pro Ser Val Ser Gln Leu Ser Val Leu Ser
 115 120 125
 Leu Ser Gly Val Met Leu Thr Asp Val Ser Pro Glu Pro Leu Gln Ala
 130 135 140
 Leu Leu Glu Arg Ala Ser Ala Thr Leu Gln Asp Leu Val Phe Asp Glu
 145 150 155 160
 Cys Gly Ile Thr Asp Asp Gln Leu Leu Ala Leu Leu Pro Ser Leu Ser
 165 170 175
 His Cys Ser Gln Leu Thr Thr Leu Ser Phe Tyr Gly Asn Ser Ile Ser
 180 185 190
 Ile Ser Ala Leu Gln Ser Leu Leu Gln His Leu Ile Gly Xaa Ser Asn
 195 200 205
 Leu Thr His Val Leu Tyr Pro Val Pro Leu Glu Ser Tyr Glu Asp Ile
 210 215 220
 His Gly Xaa Leu Xaa Leu Glu Arg Leu Leu Ser Ala Cys Gln Xaa Gln
 225 230 235 240
 Gly Val Ala Val

<210> 455

<211> 195

<212> PRT

<213> Homo sapiens

<400> 455

His Glu Gly Thr Gln Ser Phe Val Phe Gln Arg Glu Glu Ile Ala Gln
 1 5 10 15

404

Leu Ala Arg Gln Tyr Ala Gly Leu Asp His Glu Leu Ala Phe Ser Arg
 20 25 30
 Leu Ile Val Glu Leu Arg Arg Leu His Pro Gly His Val Leu Pro Asp
 35 40 45
 Glu Glu Leu Gln Trp Val Phe Val Asn Ala Gly Gly Trp Met Gly Ala
 50 55 60
 Met Cys Leu Leu His Ala Ser Leu Ser Glu Tyr Val Leu Leu Phe Gly
 65 70 75 80
 Thr Ala Leu Gly Ser Arg Gly His Ser Gly Arg Tyr Trp Ala Glu Ile
 85 90 95
 Ser Asp Thr Ile Ile Ser Gly Thr Phe His Gln Trp Arg Glu Gly Thr
 100 105 110
 Thr Lys Ser Glu Val Phe Tyr Pro Gly Glu Thr Val Val His Gly Pro
 115 120 125
 Gly Glu Ala Thr Ala Val Glu Trp Gly Pro Asn Thr Trp Met Val Glu
 130 135 140
 Tyr Gly Arg Gly Val Ile Pro Ser Thr Leu Ala Phe Ala Leu Ala Asp
 145 150 155 160
 Thr Val Phe Ser Thr Gln Asp Phe Leu Thr Leu Phe Tyr Thr Leu Arg
 165 170 175
 Ser Tyr Ala Arg Gly Leu Arg Leu Glu Leu Thr Thr Tyr Leu Phe Gly
 180 185 190
 Gln Asp Pro
 195

<210> 456

<211> 36

<212> PRT

<213> Homo sapiens

<400> 456

Leu Val Thr Leu Leu His Ala Met Gln Ala Arg Asp Lys Thr Leu Gly
 1 5 10 15
 Leu Ala Thr Leu Cys Ile Gly Gly Gly Gln Gly Ile Ala Met Val Ile
 20 25 30

405

Glu Arg Leu Asn
35

<210> 457
<211> 152
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (86)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (114)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 457
Val Thr Ala Ala Ala Ser Val Arg Ala Leu Gln Val Thr Val Ala Gly
1 5 10 15
Leu Leu Leu Val Phe Phe Leu Phe Gly Ala Pro Leu Asp Ser Leu Pro
20 25 30
Ser Met Lys Ala Leu Ser Pro Val Arg Gly Cys Tyr Glu Ala Val Cys
35 40 45
Cys Leu Ser Glu Arg Ser Leu Ala Ile Ala Arg Gly Arg Gly Lys Gly
50 55 60
Pro Ala Ala Glu Glu Pro Leu Ser Leu Leu Asp Asp Met Asn His Cys
65 70 75 80
Tyr Ser Arg Leu Arg Xaa Leu Val Pro Gly Val Pro Arg Gly Thr Gln
85 90 95
Leu Ser Gln Val Glu Ile Leu Gln Arg Val Ile Asp Tyr Ile Leu Asp
100 105 110
Leu Xaa Val Val Leu Ala Glu Pro Ala Pro Gly Pro Pro Asp Gly Pro
115 120 125
His Leu Pro Ile Gln Thr Ala Glu Leu Ala Pro Glu Leu Val Ile Ser
130 135 140
Asn Asp Lys Arg Ser Phe Cys His
145 150

<210> 458
<211> 31
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (17)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (25)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (31)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 458
Leu Leu Asn Asn Phe Ile Phe Leu Glu Thr His Tyr Leu Trp Ala Cys
1 5 10 15
Xaa Thr Trp Thr Ile Trp Pro Asn Xaa Leu Asp Lys Lys Gly Xaa
20 25 30

<210> 459
<211> 157
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (72)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (124)
<223> Xaa equals any of the naturally occurring L-amino acids

407

<220>

<221> SITE

<222> (130)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 459

Asp Pro Arg Val Arg Glu Thr Thr Val Lys Ala Arg Ala Arg Ser Gln
 1 5 10 15

His Ala Gly Gly Pro Glu Leu Gly Leu Ser Gln Xaa Tyr Val Thr Pro
 20 25 30

Arg Arg Pro Phe Glu Lys Ser Arg Leu Asp Gln Glu Leu Lys Leu Ile
 35 40 45

Gly Glu Tyr Gly Leu Arg Asn Lys Arg Glu Val Trp Arg Val Lys Phe
 50 55 60

Thr Leu Ala Lys Ile Arg Lys Xaa Ala Arg Glu Leu Leu Thr Leu Asp
 65 70 75 80

Glu Lys Asp Pro Arg Arg Leu Phe Glu Gly Asn Ala Leu Leu Arg Arg
 85 90 95

Leu Val Arg Ile Gly Val Leu Asp Glu Gly Lys Met Lys Leu Asp Tyr
 100 105 110

Ile Leu Gly Leu Lys Met Arg Ile Leu Gly Glu Xaa Ser Ala Asp Pro
 115 120 125

Gly Xaa Ser Ser Trp Gly Trp Pro Ile His Pro Pro Cys Pro Val Leu
 130 135 140

Ile Arg Gln Ala Thr Gln Val Arg Lys Gln Val Val Asn
 145 150 155

<210> 460

<211> 136

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (119)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (130)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 460

Ile Trp Ala Pro Phe Pro His His Gln Gly Ser Gly Ser Gln Val Ser
1 5 10 15

Ser Tyr Gly Thr Gly Ala Leu Lys Ser His Ile Met Ala Ala Lys Ala
20 25 30

Val Ala Asn Thr Met Arg Thr Ser Leu Gly Pro Asn Gly Leu Asp Lys
35 40 45

Met Met Val Asp Lys Asp Gly Asp Val Thr Val Thr Asn Asp Gly Ala
50 55 60

Thr Ile Leu Ser Met Met Asp Val Asp His Gln Ile Ala Lys Leu Met
65 70 75 80

Val Glu Leu Ser Lys Ser Gln Asp Asp Glu Ile Gly Asp Gly Asp His
85 90 95

Gly Gly Gly Cys Pro Gly Arg Arg Pro Ala Gly Arg Arg Pro Ser Ser
100 105 110

Cys Trp Thr Ala Ala Phe Xaa Arg Ser Gly Ser Pro Thr Val Thr Ser
115 120 125

Arg Xaa Pro Ala Leu Ala Xaa Glu
130 135

<210> 461

<211> 390

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (11)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (375)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (382)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (383)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (386)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (387)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 461
 Cys Gly Asn Trp Trp Val Pro Arg Ala Gly Xaa Asn Trp Xaa Arg Gly
 1 5 10 15
 Ser Arg Phe Leu Phe Val Asp Arg Cys Asp Arg His Leu Thr Met Gln
 20 25 30
 Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu
 35 40 45
 Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu
 50 55 60
 Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu
 65 70 75 80
 Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr
 85 90 95
 Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys
 100 105 110
 Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser Asp Thr
 115 120 125

410

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Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro
 130                135                140

Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg
145                150                155                160

Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val
                165                170                175

Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu Thr Gly
                180                185                190

Lys Thr Ile Thr Leu Glu Val Glu Pro Ser Asp Thr Ile Glu Asn Val
 195                200                205

Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg
 210                215                220

Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp
225                230                235                240

Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg
                245                250                255

Gly Gly Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr
 260                265                270

Leu Glu Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile
 275                280                285

Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala
 290                295                300

Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln
305                310                315                320

Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln
 325                330                335

Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu
 340                345                350

Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Arg Ser Arg Gln Gly Arg
 355                360                365

His Pro Pro Asp Gln Gln Xaa Leu Ile Leu Leu Gly Lys Xaa Xaa Lys
 370                375                380

Trp Xaa Xaa Pro Phe Asp
385                390

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411

<210> 462

<211> 171

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (74)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (142)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (155)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 462

Cys	Ser	Thr	Val	Arg	Ile	Pro	Gly	Ser	Thr	His	Ala	Ser	Gly	Leu	Ser
1				5					10					15	

Arg	Arg	Ala	Ser	Pro	Val	Tyr	Leu	Ala	Ser	Met	Ser	Gly	Arg	Gly	Lys
		20						25					30		

Thr	Gly	Gly	Lys	Ala	Arg	Ala	Lys	Ala	Lys	Ser	Arg	Ser	Ser	Arg	Ala
		35					40					45			

Gly	Leu	Gln	Phe	Pro	Val	Gly	Arg	Val	His	Arg	Leu	Leu	Arg	Lys	Gly
	50					55					60				

His	Tyr	Ala	Glu	Arg	Val	Gly	Ala	Gly	Xaa	Pro	Val	Tyr	Leu	Ala	Ala
65				70					75					80	

Val	Leu	Glu	Tyr	Leu	Thr	Ala	Glu	Ile	Leu	Glu	Leu	Ala	Gly	Asn	Ala
			85					90						95	

Ala	Arg	Asp	Asn	Lys	Lys	Thr	Arg	Ile	Ile	Pro	Arg	His	Leu	Gln	Leu
		100					105						110		

Ala	Ile	Arg	Asn	Asp	Glu	Glu	Leu	Asn	Lys	Leu	Leu	Gly	Gly	Val	Thr
		115					120					125			

412

Ile Ala Gln Gly Arg Arg Xaa Ala Gln His Pro Gly Arg Xaa Cys Cys
 130 135 140

Pro Arg Arg Pro Ala Pro Pro Trp Gly Arg Xaa Pro Phe Gly Gly Gln
 145 150 155 160

Glu Arg Ala Thr Lys Ala Ser Gln Gly Val Leu
 165 170

<210> 463

<211> 433

<212> PRT

<213> Homo sapiens

<400> 463

Arg Val Arg Ala Pro Pro Arg Pro Pro Leu Gly Pro Ser Arg Pro Ser
 1 5 10 15

His His Val His Pro Leu Gln Leu Pro Gly Ile Arg Glu Val Thr Ile
 20 25 30

Asn Gln Ser Leu Leu Ala Pro Leu Arg Leu Asp Ala Asp Pro Ser Leu
 35 40 45

Gln Arg Val Arg Gln Glu Glu Ser Glu Gln Ile Lys Thr Leu Asn Asn
 50 55 60

Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu Glu Gln Gln Asn
 65 70 75 80

Lys Leu Leu Glu Thr Lys Trp Thr Leu Leu Gln Glu Gln Lys Ser Ala
 85 90 95

Lys Ser Ser Arg Leu Pro Asp Ile Phe Glu Ala Gln Ile Ala Gly Leu
 100 105 110

Arg Gly Gln Leu Glu Ala Leu Gln Val Asp Gly Gly Arg Leu Glu Ala
 115 120 125

Glu Leu Arg Ser Met Gln Asp Val Val Glu Asp Phe Lys Asn Lys Tyr
 130 135 140

Glu Asp Glu Ile Asn Arg Arg Thr Ala Ala Glu Asn Glu Phe Val Val
 145 150 155 160

Leu Lys Lys Asp Val Asp Ala Ala Tyr Met Ser Lys Val Glu Leu Glu
 165 170 175

413

Ala Lys Val Asp Ala Leu Asn Asp Glu Ile Asn Phe Leu Arg Thr Leu
 180 185 190
 Asn Glu Thr Glu Leu Thr Glu Leu Gln Ser Gln Ile Ser Asp Thr Ser
 195 200 205
 Val Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp Leu Asp Gly Ile
 210 215 220
 Ile Ala Glu Val Lys Ala Gln Tyr Glu Glu Met Ala Lys Cys Ser Arg
 225 230 235 240
 Ala Glu Ala Glu Ala Trp Tyr Gln Thr Lys Phe Glu Thr Leu Gln Ala
 245 250 255
 Gln Ala Gly Lys His Gly Asp Asp Leu Arg Asn Thr Arg Asn Glu Ile
 260 265 270
 Ser Glu Met Asn Arg Ala Ile Gln Arg Leu Gln Ala Glu Ile Asp Asn
 275 280 285
 Ile Lys Asn Gln Arg Ala Lys Leu Glu Ala Ala Ile Ala Glu Ala Glu
 290 295 300
 Glu Arg Gly Glu Leu Ala Leu Lys Asp Ala Arg Ala Lys Gln Glu Glu
 305 310 315 320
 Leu Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met Ala Arg Gln Leu
 325 330 335
 Arg Glu Tyr Gln Glu Leu Met Ser Val Lys Leu Ala Leu Asp Ile Glu
 340 345 350
 Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu Ser Arg Leu Ala
 355 360 365
 Gly Asp Gly Val Gly Ala Val Asn Ile Ser Val Met Asn Ser Thr Gly
 370 375 380
 Gly Ser Ser Ser Gly Gly Gly Ile Gly Leu Thr Leu Gly Gly Thr Met
 385 390 395 400
 Gly Ser Asn Ala Leu Ser Phe Ser Ser Ser Ala Gly Pro Gly Leu Leu
 405 410 415
 Lys Ala Tyr Ser Ile Arg Thr Ala Ser Ala Ser Arg Arg Ser Ala Arg
 420 425 430

Asp

<210> 464
 <211> 121
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (50)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (64)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (110)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (114)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (115)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (117)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 464
 Gly Ser Gly Cys Val Phe Ala Ile Leu Gly Arg Arg Cys Ser Arg Pro
 1 5 10 15
 Trp Arg Ile Trp Pro Gly Glu Pro Leu Gln Arg Ala Pro Pro Ala Ala
 20 25 30
 Gly Thr Arg Trp Pro His Gly His Arg Ser Ser Pro Val Gly Thr Pro
 35 40 45
 Gly Xaa Ala Pro Asn Val Pro Ala Ile Trp Gln Gln Pro Leu Trp Xaa
 50 55 60
 Glu Tyr Ser Cys Glu Tyr Gly Ser Met Lys Phe Tyr Ala Leu Cys Gly

415

65					70					75					80	
Phe	Gly	Gly	Val	Leu	Ser	Cys	Gly	Leu	Thr	His	Thr	Ala	Val	Val	Pro	
				85					90					95		
Leu	Asp	Leu	Val	Lys	Cys	Arg	Met	Gln	Val	Asp	Pro	Gln	Xaa	Tyr	Lys	
				100					105					110		
Gly	Xaa	Xaa	Asn	Xaa	Ile	Leu	Ile	Asn								
				115					120							

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<210> 465
<211> 68
<212> PRT
<213> Homo sapiens
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<400> 465
Arg Ile Pro Ala Pro Ala Ser Ser Arg His Ser Gly Gly Arg Cys Ala
  1                      5                      10                      15
Ala Gly Pro Arg Gly Pro Pro Ala Thr Ala Ser Arg Ala Leu Arg Ala
      20                      25                      30
Val His Arg Pro Leu Asp Ala Ala Arg Gly Arg Thr Gly Ser Thr Ser
      35                      40                      45
His Leu Cys Ser Ser Ser Tyr Thr Ile Gly Cys Leu Leu Trp Phe Ser
      50                      55                      60
Gln Lys Ala Met
      65

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<210> 466
<211> 224
<212> PRT
<213> Homo sapiens
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```

<400> 466
Ala Thr Ile Leu Glu Arg Glu Ala Glu Gln Ser Arg Leu Gly Ala Thr
 1               5               10               15
Glu Arg Ala Ala Ala Ala Ala Met Asn Pro Glu Tyr Asp Tyr Leu Phe
      20               25               30
Lys Leu Leu Leu Ile Gly Asp Ser Gly Val Gly Lys Ser Cys Leu Leu
 35               40               45

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416

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Leu Arg Phe Ala Asp Asp Thr Tyr Thr Glu Ser Tyr Ile Ser Thr Ile
 50                      55                      60

Gly Val Asp Phe Lys Ile Arg Thr Ile Glu Leu Asp Gly Lys Thr Ile
 65                      70                      75                      80

Lys Leu Gln Ile Trp Asp Thr Ala Gly Gln Glu Arg Phe Arg Thr Ile
                      85                      90                      95

Thr Ser Ser Tyr Tyr Arg Gly Ala His Gly Ile Ile Val Val Tyr Asp
          100                      105                      110

Val Thr Asp Gln Glu Ser Tyr Ala Asn Val Lys Gln Trp Leu Gln Glu
          115                      120                      125

Ile Asp Arg Tyr Ala Ser Glu Asn Val Asn Lys Leu Leu Val Gly Asn
 130                      135                      140

Lys Ser Asp Leu Thr Thr Lys Lys Val Val Asp Asn Thr Thr Ala Lys
 145                      150                      155                      160

Glu Phe Ala Asp Ser Leu Gly Ile Pro Phe Leu Glu Thr Ser Ala Lys
          165                      170                      175

Asn Ala Thr Asn Val Glu Gln Ala Phe Met Thr Met Ala Ala Glu Ile
          180                      185                      190

Lys Lys Arg Met Gly Pro Gly Ala Ala Ser Gly Gly Glu Arg Pro Asn
          195                      200                      205

Leu Lys Ile Asp Ser Thr Pro Val Lys Pro Ala Gly Gly Gly Cys Cys
 210                      215                      220

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<210> 467

<211> 76

<212> PRT

<213> Homo sapiens

<400> 467

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Ser Glu Ala Pro Gly Glu Ser Val Gly Thr Thr Pro Glu Ala Gln Met
 1                      5                      10                      15

Lys Thr Gly Pro Phe Ala Glu His Ser Asn Gln Leu Trp Asn Ile Ser
          20                      25                      30

Ala Val Pro Ser Trp Ser Lys Val Asn Gln Gly Leu Ile Arg Met Tyr

```

417

35 40 45
 Lys Ala Glu Cys Leu Glu Lys Phe Pro Val Ile Gln His Phe Lys Phe
 50 55 60
 Gly Ser Leu Leu Pro Ile His Pro Val Thr Ser Gly
 65 70 75

<210> 468
 <211> 111
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (31)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (35)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (47)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (49)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (78)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (97)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 468
 Ser Leu Ala Arg Thr Gly Pro Arg Ser Leu Ala Arg Pro Cys Arg Arg
 1 5 10 15

Arg Pro Ala His Arg His Pro Leu Gln Pro Cys Pro Pro Gly Xaa Cys
 20 25 30

Pro	Arg	Xaa	Pro	Thr	Ala	Asp	Val	Arg	Arg	Pro	Arg	His	Arg	Xaa	Arg	
35						40						45				
Xaa	Glu	Leu	His	Ala	His	Asn	Val	Thr	Ser	Pro	Pro	Ala	Pro	Thr	Ala	
50						55						60				
Trp	Ala	Ala	Pro	Ala	Pro	Gln	His	Gln	Pro	Gln	Pro	Leu	Xaa	Leu	Val	
65						70						75			80	
Pro	Gly	Arg	Arg	Val	Cys	Ser	Arg	Leu	Leu	Pro	Arg	Cys	Ala	Cys	Gly	
			85						90						95	
Xaa	Cys	Cys	Pro	Gly	Val	Ala	Leu	Ala	Gly	Arg	Ile	Pro	Trp	Asn		
			100						105						110	

<210> 469

<211> 459

<212> PRT

<213> Homo sapiens

<400> 469

Pro	Arg	Val	Arg	Pro	Arg	Val	Arg	Pro	Arg	Val	Arg	Leu	Ser	Ser	Pro
1				5					10					15	
Ser	Pro	Val	Cys	Leu	Pro	Pro	Ala	Ala	Ala	Thr	Met	Thr	Thr	Ser	Ile
			20					25					30		
Arg	Gln	Phe	Thr	Ser	Ser	Ser	Ser	Ile	Lys	Gly	Ser	Ser	Gly	Leu	Gly
		35					40					45			
Gly	Gly	Ser	Ser	Arg	Thr	Ser	Cys	Arg	Leu	Ser	Gly	Gly	Leu	Gly	Ala
	50					55					60				
Gly	Ser	Cys	Arg	Leu	Gly	Ser	Ala	Gly	Gly	Leu	Gly	Ser	Thr	Leu	Gly
65					70					75					80
Gly	Ser	Ser	Tyr	Ser	Ser	Cys	Tyr	Ser	Phe	Gly	Ser	Gly	Gly	Gly	Tyr
			85						90					95	
Gly	Ser	Ser	Phe	Gly	Gly	Val	Asp	Gly	Leu	Leu	Ala	Gly	Gly	Glu	Lys
			100					105					110		
Ala	Thr	Met	Gln	Asn	Leu	Asn	Asp	Arg	Leu	Ala	Ser	Tyr	Leu	Asp	Lys
		115					120					125			
Val	Arg	Ala	Leu	Glu	Glu	Ala	Asn	Thr	Glu	Leu	Glu	Val	Lys	Ile	Arg
130						135					140				

Asp Trp Tyr Gln Arg Gln Ala Pro Gly Pro Ala Arg Asp Tyr Ser Gln
 145 150 155 160
 Tyr Tyr Arg Thr Ile Glu Glu Leu Gln Asn Lys Ile Leu Thr Ala Thr
 165 170 175
 Val Asp Asn Ala Asn Ile Leu Leu Gln Ile Asp Asn Ala Arg Leu Ala
 180 185 190
 Ala Asp Asp Phe Arg Thr Lys Phe Glu Thr Glu Gln Ala Leu Arg Leu
 195 200 205
 Ser Val Glu Ala Asp Ile Asn Gly Leu Arg Arg Val Leu Asp Glu Leu
 210 215 220
 Thr Leu Ala Arg Ala Asp Leu Glu Met Gln Ile Glu Asn Leu Lys Glu
 225 230 235 240
 Glu Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Met Asn Ala Leu
 245 250 255
 Arg Gly Gln Val Gly Gly Glu Ile Asn Val Glu Met Asp Ala Ala Pro
 260 265 270
 Gly Val Asp Leu Ser Arg Ile Leu Asn Glu Met Arg Asp Gln Tyr Glu
 275 280 285
 Lys Met Ala Glu Lys Asn Arg Lys Asp Ala Glu Asp Trp Phe Phe Ser
 290 295 300
 Lys Thr Glu Glu Leu Asn Arg Glu Val Ala Thr Asn Ser Glu Leu Val
 305 310 315 320
 Gln Ser Gly Lys Ser Glu Ile Ser Glu Leu Arg Arg Thr Met Gln Ala
 325 330 335
 Leu Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ser Leu Glu
 340 345 350
 Gly Asn Leu Ala Glu Thr Glu Asn Arg Tyr Cys Val Gln Leu Ser Gln
 355 360 365
 Ile Gln Gly Leu Ile Gly Ser Val Glu Glu Gln Leu Ala Gln Leu Arg
 370 375 380
 Cys Glu Met Glu Gln Gln Asn Gln Glu Tyr Lys Ile Leu Leu Asp Val
 385 390 395 400
 Lys Thr Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu
 405 410 415

420

Gly Glu Asp Ala His Leu Thr Gln Tyr Lys Lys Glu Pro Val Thr Thr
 420 425 430

Arg Gln Val Arg Thr Ile Val Glu Glu Val Gln Asp Gly Lys Val Ile
 435 440 445

Ser Ser Arg Glu Gln Val His Gln Thr Thr Arg
 450 455

<210> 470

<211> 158

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (158)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 470

Pro Pro Pro Pro Pro Pro Pro Glu Leu Cys Ser Met Ala Ser Arg Arg
 1 5 10 15

Met Glu Thr Lys Pro Val Ile Thr Cys Leu Lys Thr Leu Leu Ile Ile
 20 25 30

Tyr Ser Phe Val Phe Trp Ile Thr Gly Val Ile Leu Leu Ala Val Gly
 35 40 45

Val Trp Gly Lys Leu Thr Leu Gly Thr Tyr Ile Ser Leu Ile Ala Glu
 50 55 60

Asn Ser Thr Asn Ala Pro Tyr Val Leu Ile Gly Thr Gly Thr Thr Ile
 65 70 75 80

Val Val Phe Gly Leu Phe Gly Cys Phe Ala Thr Cys Arg Gly Ser Pro
 85 90 95

Trp Met Leu Lys Leu Tyr Ala Met Phe Leu Ser Leu Val Phe Leu Ala
 100 105 110

Glu Leu Val Ala Gly Ile Ser Gly Phe Val Phe Arg His Glu Ile Lys
 115 120 125

Asp Thr Phe Leu Arg Thr Tyr Thr Asp Ala Met Gln Thr Tyr Asn Gly
 130 135 140

Asn Asp Glu Arg Ser Arg Ala Val Asp His Val Gln Arg Xaa
 145 150 155

421

<210> 471

<211> 59

<212> PRT

<213> Homo sapiens

<400> 471

Val Leu Phe Phe Tyr Glu Cys Pro Asn Leu Cys Phe Pro Leu Pro Ser
1 5 10 15

Gln Thr Val Trp Pro Val Glu Ser Val Trp Phe Val Phe Ile Ser Pro
20 25 30

Ser Phe Leu Glu Gln Gly Leu Arg Pro Cys His Ile Ser Tyr Ala Leu
35 40 45

His Pro Arg Leu Phe Trp Thr Leu Lys Val Asp
50 55

<210> 472

<211> 320

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (48)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (53)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (105)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 472

Asp Pro Asp Glu Val Phe Pro Val Cys Leu Pro Leu Thr Gly Asp Ala
1 5 10 15

422

Gly Glu Asp Gly Gly Lys Met Leu His Leu Pro Glu Trp Pro Glu Gln
 20 25 30

Pro Pro Gly Gly Pro Ala Ala Leu Gln Val Arg Gly Ala Glu Asp Xaa
 35 40 45

Xaa Leu Ser Phe Xaa Asp Cys Glu Ser Leu Gln Ala Val Phe Asp Pro
 50 55 60

Ala Ser Cys Pro His Met Leu Arg Ala Pro Ala Arg Val Leu Gly Glu
 65 70 75 80

Ala Val Leu Pro Phe Ser Pro Ala Leu Ala Glu Val Thr Leu Gly Ile
 85 90 95

Gly Arg Gly Ala Gly Ser Ser Trp Xaa Tyr His Glu Glu Glu Ala Asp
 100 105 110

Ser Thr Ala Lys Ala Met Val Thr Glu Met Cys Leu Gly Glu Glu Asp
 115 120 125

Phe Gln Gln Leu Gln Ala Gln Glu Gly Val Ala Ile Thr Phe Cys Leu
 130 135 140

Lys Glu Phe Arg Gly Leu Leu Ser Phe Ala Glu Ser Ala Asn Leu Asn
 145 150 155 160

Leu Ser Ile His Phe Asp Ala Pro Gly Arg Pro Ala Ile Phe Thr Ile
 165 170 175

Lys Asp Ser Leu Leu Asp Gly His Phe Val Leu Ala Thr Leu Ser Asp
 180 185 190

Thr Asp Ser His Ser Gln Asp Leu Gly Ser Pro Glu Arg His Gln Pro
 195 200 205

Val Pro Gln Leu Gln Ala His Ser Thr Pro His Pro Asp Asp Phe Ala
 210 215 220

Asn Asp Asp Ile Asp Ser Tyr Met Ile Ala Met Glu Thr Thr Ile Gly
 225 230 235 240

Asn Glu Gly Ser Arg Val Leu Pro Ser Ile Ser Leu Ser Pro Gly Pro
 245 250 255

Gln Pro Pro Lys Ser Pro Gly Pro His Ser Glu Glu Glu Asp Glu Ala
 260 265 270

Glu Pro Ser Thr Val Pro Gly Thr Pro Pro Pro Lys Lys Phe Arg Ser
 275 280 285

423

Leu Phe Phe Gly Ser Ile Leu Ala Pro Val Arg Ser Pro Gln Gly Pro
 290 295 300

Ser Leu Cys Trp Arg Lys Thr Val Arg Val Lys Ala Glu Pro Arg Thr
 305 310 315 320

<210> 473

<211> 331

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (283)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (299)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (324)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 473

Pro Pro Cys Ala Val Pro Gly Pro Arg Leu Ser Pro Lys Leu Arg Thr
 1 5 10 15

Pro Ser Asn Ser Arg Glu Ser Xaa Ile Cys Val Ser Gly Arg Ala Glu
 20 25 30

Ala Leu Thr Phe Arg His Gly Ala Glu Gly Ser Asp Arg Arg Gln
 35 40 45

Arg Arg Glu Gly Val Leu Gly Pro Ala Leu Leu Cys Arg Pro Trp Glu
 50 55 60

Val Leu Gly Ala His Glu Val Pro Ser Arg Asn Ile Phe Ser Glu Gln

424

65		70		75		80									
Thr	Ile	Pro	Pro	Ser	Ala	Lys	Tyr	Gly	Gly	Arg	His	Thr	Val	Thr	Met
				85					90					95	
Ile	Pro	Gly	Asp	Gly	Ile	Gly	Pro	Glu	Leu	Met	Leu	His	Val	Lys	Ser
			100					105					110		
Val	Phe	Arg	His	Ala	Cys	Val	Pro	Val	Asp	Phe	Glu	Glu	Val	His	Val
			115					120				125			
Ser	Ser	Asn	Ala	Asp	Glu	Glu	Asp	Ile	Arg	Asn	Ala	Ile	Met	Ala	Ile
			130				135				140				
Arg	Arg	Asn	Arg	Val	Ala	Leu	Lys	Gly	Asn	Ile	Glu	Thr	Asn	His	Asn
					150					155					160
Leu	Pro	Pro	Ser	His	Lys	Ser	Arg	Asn	Asn	Ile	Leu	Arg	Thr	Ser	Leu
				165					170					175	
Asp	Leu	Tyr	Ala	Asn	Val	Ile	His	Cys	Lys	Ser	Leu	Pro	Gly	Val	Val
			180					185					190		
Thr	Arg	His	Lys	Asp	Ile	Asp	Ile	Leu	Ile	Val	Arg	Glu	Asn	Thr	Glu
			195					200				205			
Gly	Glu	Tyr	Ser	Ser	Leu	Glu	His	Glu	Ser	Val	Ala	Gly	Val	Val	Glu
			210				215				220				
Ser	Leu	Lys	Ile	Ile	Thr	Lys	Ala	Lys	Ser	Leu	Arg	Ile	Ala	Glu	Tyr
					230					235				240	
Ala	Phe	Lys	Leu	Ala	Gln	Glu	Ser	Gly	Arg	Lys	Lys	Val	Thr	Ala	Val
				245					250					255	
His	Lys	Ala	Asn	Ile	Met	Lys	Leu	Gly	Asp	Gly	Leu	Phe	Leu	Gln	Cys
			260					265					270		
Cys	Arg	Glu	Val	Ala	Ala	Arg	Tyr	Pro	Gln	Xaa	Thr	Phe	Glu	Asn	Met
			275					280				285			
Ile	Val	Asp	Asn	Thr	Thr	Met	Gln	Leu	Val	Xaa	Arg	Pro	Gln	Gln	Phe
			290				295				300				
Asp	Val	Met	Val	Met	Pro	Asn	Leu	Tyr	Gly	Asn	Ile	Val	Lys	Gln	Cys
			305			310				315				320	
Leu	Arg	Gly	Xaa	Gly	Arg	Gly	Pro	Lys	Leu	Val					
				325					330						

425

<210> 474

<211> 30

<212> PRT

<213> Homo sapiens

<400> 474

Thr Pro Ile Ser Thr Lys Asn Thr Lys Ile Ser Gln Ala Arg Trp Arg
 1 5 10 15

Ala His Val Val Pro Ala Thr Arg Glu Ala Asp Ala Glu Glu
 20 25 30

<210> 475

<211> 124

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (110)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 475

Thr Gln Phe Ser Leu Ser Pro Val Glu Thr Ile Tyr Thr Ile Leu Cys
 1 5 10 15

Ile Asn Val Tyr Thr Leu Pro Ile Cys Ile His Ile Tyr Ile Val Tyr
 20 25 30

Ile Leu Tyr Met Tyr Arg Cys Val Tyr Val His Ile Tyr Thr His Ala
 35 40 45

His Asn Lys Ile Arg Cys Ser Leu Gln Ile Gln Met Leu Ile Thr Lys
 50 55 60

Pro Asp Ala Thr Gln Thr Ala Ala Glu Glu Thr Arg Leu Asp Ser Cys
 65 70 75 80

Asn Arg Ser Gln Lys Ile Lys Thr Ala Thr Cys Ser Asp Phe Gly His
 85 90 95

Phe Cys Met Phe Ile Lys Asn Gly Phe Val Thr Arg Lys Xaa Arg Thr
 100 105 110

Ser Val Ser Glu Lys Gly Arg Trp Gly Glu Pro Ser
 115 120

426

<210> 476

<211> 64

<212> PRT

<213> Homo sapiens

<400> 476

Asn Gly Tyr Leu Val Phe Pro Arg Lys Asn Ser Phe Leu Leu Ile Phe
 1 5 10 15

Gly Leu Phe Val Tyr Leu Glu Thr Asn Leu Asp Ser Leu Pro Leu Val
 20 25 30

Asp Thr His Ser Lys Arg Thr Leu Leu Ile Lys Thr Val Glu Thr Arg
 35 40 45

Asp Gly Gln Val Ile Asn Glu Thr Ser Gln His His Asp Asp Leu Glu
 50 55 60

<210> 477

<211> 107

<212> PRT

<213> Homo sapiens

<400> 477

Val Leu Thr Val Asp Ala Arg Asn His Gly Asp Ser Pro His Ser Pro
 1 5 10 15

Asp Met Ser Tyr Glu Ile Met Ser Gln Asp Leu Gln Asp Leu Leu Pro
 20 25 30

Gln Leu Gly Leu Val Pro Cys Val Val Val Gly His Ser Met Gly Gly
 35 40 45

Lys Thr Ala Met Leu Leu Ala Leu Gln Arg Pro Glu Leu Val Glu Arg
 50 55 60

Leu Ile Ala Val Asp Ile Ser Pro Val Glu Ser Thr Gly Val Ser His
 65 70 75 80

Phe Ala Thr Tyr Val Ala Ala Met Arg Ala Ile Asn Ile Ala Asp Arg
 85 90 95

Leu Ala Pro Leu Pro Cys Pro Lys Thr Gly Gly
 100 105

427

<210> 478

<211> 282

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (281)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 478

Arg Glu Leu Gly Gly Thr Leu Leu Ser Ala Ile Glu Val Glu Gly Ala
 1 5 10 15

Lys Met Gln Ser Asn Lys Thr Phe Asn Leu Glu Lys Gln Asn His Thr
 20 25 30

Pro Arg Lys His His Gln His His His Gln Gln Gln His His Gln Gln
 35 40 45

Gln Gln Gln Gln Pro Pro Pro Pro Pro Ile Pro Ala Asn Gly Gln Gln
 50 55 60

Ala Ser Ser Gln Asn Glu Gly Leu Thr Ile Asp Leu Lys Asn Phe Arg
 65 70 75 80

Lys Pro Gly Glu Lys Thr Phe Thr Gln Arg Ser Arg Leu Phe Val Gly
 85 90 95

Asn Leu Pro Pro Asp Ile Thr Glu Glu Glu Met Arg Lys Leu Phe Glu
 100 105 110

Lys Tyr Gly Lys Ala Gly Glu Val Phe Ile His Lys Asp Lys Gly Phe
 115 120 125

Gly Phe Ile Arg Leu Glu Thr Arg Thr Leu Ala Glu Ile Ala Lys Val
 130 135 140

Glu Leu Asp Asn Met Pro Leu Arg Gly Lys Gln Leu Arg Val Arg Phe
 145 150 155 160

Ala Cys His Ser Ala Ser Leu Thr Val Arg Asn Leu Pro Gln Tyr Val
 165 170 175

Ser Asn Glu Leu Leu Glu Glu Ala Phe Ser Val Phe Gly Gln Val Glu
 180 185 190

Arg Ala Val Val Ile Val Asp Asp Arg Gly Arg Pro Ser Gly Lys Gly
 195 200 205

428

Ile Val Glu Phe Ser Gly Lys Pro Ala Ala Arg Lys Ala Leu Asp Arg
 210 215 220

Cys Ser Glu Gly Ser Phe Leu Leu Thr Thr Phe Pro Arg Pro Val Thr
 225 230 235 240

Val Glu Pro Met Asp Gln Leu Asp Asp Glu Glu Gly Leu Pro Glu Lys
 245 250 255

Leu Val Ile Lys Asn Gln Gln Phe His Lys Glu Arg Glu Gln Pro Pro
 260 265 270

Arg Phe Ala Gln Pro Gly Ser Phe Xaa Val
 275 280

<210> 479

<211> 289

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (206)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (215)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (218)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (285)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 479

Ala Val Pro Val Arg Asn Ser Arg Val Asp Pro Arg Val Arg Val Cys
 1 5 10 15

Gly Pro Leu Ser Ala Pro Arg Gly Ser Arg Arg Pro Thr Val Pro Gly
 20 25 30

Thr Pro Ala Cys Leu Ala Arg Pro Ala Ala Gln Gly Phe Ser Ala Ala

429

35	40	45
Leu Pro Val Arg Trp Thr Gly Arg Arg Ala Gly Pro Ser Arg Pro Val		
50	55	60
Pro Ile Gly Thr Pro Ser Arg Ala Ala Asp Pro Ser Gln Gly Glu Met		
65	70	75
Ser Ala Asp Ala Ala Ala Gly Ala Pro Leu Pro Arg Leu Cys Cys Leu		
85	90	95
Glu Lys Gly Pro Asn Gly Tyr Gly Phe His Leu His Gly Glu Lys Gly		
100	105	110
Lys Leu Gly Gln Tyr Ile Arg Leu Val Glu Pro Gly Ser Pro Ala Glu		
115	120	125
Lys Ala Gly Leu Leu Ala Gly Asp Arg Leu Val Glu Val Asn Gly Glu		
130	135	140
Asn Val Glu Lys Glu Thr His Gln Gln Val Val Ser Arg Ile Arg Ala		
145	150	155
Ala Leu Asn Ala Val Arg Leu Leu Val Val Asp Pro Glu Thr Asp Glu		
165	170	175
Gln Leu Gln Lys Leu Gly Val Gln Val Arg Glu Glu Leu Leu Arg Ala		
180	185	190
Gln Glu Ala Pro Gly Gln Ala Glu Pro Pro Ala Ala Ala Xaa Val Gln		
195	200	205
Gly Ala Gly Asn Glu Asn Xaa Pro Arg Xaa Ala Asp Lys Ser His Pro		
210	215	220
Glu Gln Arg Glu Leu Arg Pro Arg Leu Cys Thr Met Lys Lys Gly Pro		
225	230	235
Ser Gly Tyr Gly Phe Asn Leu His Ser Asp Lys Ser Lys Pro Gly Gln		
245	250	255
Phe Ile Arg Ser Val Asp Pro Asp Ser Pro Ala Glu Ala Ser Gly Leu		
260	265	270
Arg Ala Gln Asp Arg Ile Val Glu Val Met Leu Leu Xaa Ser Leu Pro		
275	280	285
Ile		

430

<210> 480

<211> 44

<212> PRT

<213> Homo sapiens

<400> 480

Gly Ser Thr His Ala Ser Gly Arg Asn Glu Gly Pro Pro Ala Lys Thr
 1 5 10 15

Lys Ser Trp Val Gly Pro Thr Leu His Phe His Arg Lys Ser Glu His
 20 25 30

Leu Val Gly Leu Lys Val Leu Cys Cys Phe Arg Leu
 35 40

<210> 481

<211> 124

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (3)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 481

Ser Ile Xaa His Xaa Arg Lys Xaa Xaa Xaa Thr Val Arg Ser Asp Ser
 1 5 10 15

431

Arg Val Asp Pro Arg Ser Asp Asp Phe Thr Pro Leu Glu Ile Leu Trp
 20 25 30
 Thr Phe Ser Ile Tyr Leu Glu Ser Val Ala Ile Leu Pro Gln Leu Phe
 35 40 45
 Met Val Ser Lys Thr Gly Glu Ala Glu Thr Ile Thr Ser His Tyr Leu
 50 55 60
 Phe Ala Leu Gly Val Tyr Arg Thr Leu Tyr Leu Phe Asn Trp Ile Trp
 65 70 75 80
 Arg Tyr His Phe Glu Gly Phe Phe Asp Leu Ile Ala Ile Val Ala Gly
 85 90 95
 Leu Val Gln Thr Val Leu Tyr Cys Asp Phe Phe Tyr Leu Tyr Ile Thr
 100 105 110
 Lys Val Leu Lys Gly Lys Lys Leu Ser Leu Pro Ala
 115 120

<210> 482

<211> 131

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (122)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (124)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (127)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (131)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 482

Cys Ser Ser Arg Gly Ala His His Ser His Cys Asp Arg Leu Pro His

432

```

      1             5             10             15
Ser Pro Trp Pro Gly Leu Arg Glu Val Glu Leu Leu Ala Ser Val His
      20             25             30
Thr Glu Gln Met Glu Glu Glu Leu Ala Leu Gly Pro Arg Gly Gln Gly
      35             40             45
Gly Ala Ser Leu Ala Gly Arg Asp Gly Arg Ser Ala Gly Ala Gly Ser
      50             55             60
Tyr Gly Ala Leu Ala Asn Ser Ala Trp Gly Gly Pro Arg Lys Val Ala
      65             70             75             80
Ser Ala Ser Ala Ala Ala Ser Thr Leu Ser Glu Pro Pro Arg Arg Thr
      85             90             95
Gln Glu Ser Arg Thr Arg Thr Arg Ala Leu Gly Leu Pro Thr Leu Pro
      100            105            110
Met Glu Lys Leu Ala Ala Ser Asn Arg Xaa Pro Xaa Gly Leu Xaa Gly
      115            120            125
Pro Gly Xaa
      130

```

<210> 483

<211> 221

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (168)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (174)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 483

```

Lys Lys Pro Pro Ile Thr His Pro Ser Thr Pro Ala Glu Glu Thr Tyr
  1             5             10             15

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Asn Leu Gly Arg Gln Val Leu Pro Leu Ser Ala Val Thr Tyr Phe Gln
      20             25             30

```

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Lys Ser Gly Pro Gly Leu Leu Pro Ala Pro Ala Thr Gln Ser Ala Ser

```

433

35	40	45
Val Ala Gly Thr Leu Gln Asn Ser Leu Cys Ser Gln Val Thr Lys Lys		
50	55	60
Lys Arg Ala Asn Met Leu Val Leu Leu Ala Gly Ile Phe Val Val His		
65	70	75 80
Ile Ala Thr Val Ile Met Leu Phe Val Ser Thr Ile Ala Asn Val Trp		
85	90	95
Leu Val Ser Asn Thr Val Asp Ala Ser Val Gly Leu Trp Lys Asn Cys		
100	105	110
Thr Asn Ile Ser Cys Ser Asp Ser Leu Ser Tyr Ala Ser Glu Asp Ala		
115	120	125
Leu Lys Thr Val Gln Ala Phe Met Ile Leu Ser Ile Ile Phe Cys Val		
130	135	140
Ile Ala Leu Leu Val Phe Val Phe Gln Leu Phe Thr Met Glu Lys Gly		
145	150	155 160
Asn Arg Phe Phe Leu Ser Gly Xaa Thr Thr Leu Val Cys Xaa Leu Cys		
165	170	175
Ile Leu Val Gly Cys Pro Ser Thr Leu Val Ile Met Arg Ile Val Met		
180	185	190
Glu Arg Ile Cys Thr Thr Ala Ile Pro Thr Ser Trp Ala Gly Ser Ala		
195	200	205
Ser Ala Ser Ala Ser Ser Ser Ala Phe Ser Ile Trp Ser		
210	215	220

<210> 484

<211> 382

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (54)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (69)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (287)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (298)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (324)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (358)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 484

Thr	Lys	Leu	Trp	Thr	Leu	Val	Ser	Asn	Pro	Asp	Thr	Asp	Ala	Leu	Ile
1				5					10					15	

Cys	Trp	Ser	Pro	Ser	Xaa	Asn	Ser	Phe	His	Val	Phe	Asp	Gln	Gly	Gln
			20					25					30		

Phe	Ala	Lys	Glu	Val	Leu	Pro	Lys	Tyr	Phe	Lys	His	Asn	Asn	Met	Ala
		35					40					45			

Ser	Phe	Val	Arg	Gln	Xaa	Asn	Met	Tyr	Gly	Phe	Arg	Lys	Val	Val	His
	50					55					60				

Ile	Glu	Gln	Gly	Xaa	Leu	Val	Lys	Pro	Glu	Arg	Asp	Asp	Thr	Glu	Phe
65					70					75				80	

Gln	His	Pro	Cys	Phe	Leu	Arg	Gly	Gln	Glu	Gln	Leu	Leu	Glu	Asn	Ile
				85					90					95	

Lys	Arg	Lys	Val	Thr	Ser	Val	Ser	Thr	Leu	Lys	Ser	Glu	Asp	Ile	Lys
			100					105					110		

Ile	Arg	Gln	Asp	Ser	Val	Thr	Lys	Leu	Leu	Thr	Asp	Val	Gln	Leu	Met
		115					120					125			

435

Lys Gly Lys Gln Glu Cys Met Asp Ser Lys Leu Leu Ala Met Lys His
 130 135 140
 Glu Asn Glu Ala Leu Trp Arg Glu Val Ala Ser Leu Arg Gln Lys His
 145 150 155 160
 Ala Gln Gln Gln Lys Val Val Asn Lys Leu Ile Gln Phe Leu Ile Ser
 165 170 175
 Leu Val Gln Ser Asn Arg Ile Leu Gly Val Lys Arg Lys Ile Pro Leu
 180 185 190
 Met Leu Asn Asp Ser Gly Ser Ala His Ser Met Pro Lys Tyr Ser Arg
 195 200 205
 Gln Phe Ser Leu Glu His Val His Gly Ser Gly Pro Tyr Ser Ala Pro
 210 215 220
 Ser Pro Ala Tyr Ser Ser Ser Ser Leu Tyr Ala Pro Asp Ala Val Ala
 225 230 235 240
 Ser Ser Gly Pro Ile Ile Ser Asp Ile Thr Glu Leu Ala Pro Ala Ser
 245 250 255
 Pro Met Ala Ser Pro Gly Gly Ser Ile Asp Glu Arg Pro Leu Ser Ser
 260 265 270
 Ser Pro Leu Val Arg Val Lys Glu Glu Pro Pro Ser Pro Pro Xaa Ser
 275 280 285
 Pro Arg Val Glu Glu Ala Ser Pro Gly Xaa Pro Ser Ser Val Asp Thr
 290 295 300
 Leu Leu Ser Pro Thr Ala Leu Ile Asp Ser Ile Leu Arg Glu Ser Glu
 305 310 315 320
 Pro Ala Pro Xaa Ser Val Thr Ala Leu Thr Asp Ala Arg Gly His Thr
 325 330 335
 Asp Thr Glu Gly Arg Pro Pro Ser Pro Pro Pro Thr Ser Thr Pro Glu
 340 345 350
 Lys Cys Leu Ser Val Xaa Ala Trp Thr Arg Met Ser Ser Val Thr Thr
 355 360 365
 Trp Met Leu Trp Thr Pro Thr Trp Ile Thr Cys Arg Pro Cys
 370 375 380

<210> 485

436

<211> 416

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (399)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 485

Pro Ser Val Ala Asn Val Gly Ser His Cys Asp Leu Ser Leu Lys Ile
 1 5 10 15

Pro Glu Ile Ser Ile Gln Asp Met Thr Ala Gln Val Thr Ser Pro Ser
 20 25 30

Gly Lys Thr His Glu Ala Glu Ile Val Glu Gly Glu Asn His Thr Tyr
 35 40 45

Cys Ile Arg Phe Val Pro Ala Glu Met Gly Thr His Thr Val Ser Val
 50 55 60

Lys Tyr Lys Gly Gln His Val Pro Gly Ser Pro Phe Gln Phe Thr Val
 65 70 75 80

Gly Pro Leu Gly Glu Gly Gly Ala His Lys Val Arg Ala Gly Gly Pro
 85 90 95

Gly Leu Glu Arg Ala Glu Ala Gly Val Pro Ala Glu Phe Ser Ile Trp
 100 105 110

Thr Arg Glu Ala Gly Ala Gly Gly Leu Ala Ile Ala Val Glu Gly Pro
 115 120 125

Ser Lys Ala Glu Ile Ser Phe Glu Asp Arg Lys Asp Gly Ser Cys Gly
 130 135 140

Val Ala Tyr Val Val Gln Glu Pro Gly Asp Tyr Glu Val Ser Val Lys
 145 150 155 160

Phe Asn Glu Glu His Ile Pro Asp Ser Pro Phe Val Val Pro Val Ala
 165 170 175

Ser Pro Ser Gly Asp Ala Arg Arg Leu Thr Val Ser Ser Leu Gln Glu
 180 185 190

Ser Gly Leu Lys Val Asn Gln Pro Ala Ser Phe Ala Val Ser Leu Asn
 195 200 205

Gly Ala Lys Gly Ala Ile Asp Ala Lys Val His Ser Pro Ser Gly Ala
 210 215 220

437

Leu Glu Glu Cys Tyr Val Thr Glu Ile Asp Gln Asp Lys Tyr Ala Val
 225 230 235 240
 Arg Phe Ile Pro Arg Glu Asn Gly Val Tyr Leu Ile Asp Val Lys Phe
 245 250 255
 Asn Gly Thr His Ile Pro Gly Ser Pro Phe Lys Ile Arg Val Gly Glu
 260 265 270
 Pro Gly His Gly Gly Asp Pro Gly Leu Val Ser Ala Tyr Gly Ala Gly
 275 280 285
 Leu Glu Gly Gly Val Thr Gly Asn Pro Ala Glu Phe Val Val Asn Thr
 290 295 300
 Ser Asn Ala Gly Ala Gly Ala Leu Ser Val Thr Ile Asp Gly Pro Ser
 305 310 315 320
 Lys Val Lys Met Asp Cys Gln Glu Cys Pro Glu Gly Tyr Arg Val Thr
 325 330 335
 Tyr Thr Pro Met Ala Pro Gly Ser Tyr Leu Ile Ser Ile Lys Tyr Gly
 340 345 350
 Gly Pro Tyr His Ile Gly Gly Ser Pro Phe Lys Ala Lys Val Thr Gly
 355 360 365
 Pro Arg Leu Val Ser Asn His Ser Leu His Glu Thr Ser Ser Val Phe
 370 375 380
 Val Asp Ser Leu Thr Lys Ala Thr Cys Ala Pro Gln His Gly Xaa Pro
 385 390 395 400
 Gly Pro Gly Pro Ala Asp Ala Ser Lys Val Val Ala Lys Gly Trp Gly
 405 410 415

<210> 486

<211> 46

<212> PRT

<213> Homo sapiens

<400> 486

Phe Val Thr Ser Gly Lys Ile Ser Leu Tyr Val Tyr Ile Leu Thr Ile
 1 5 10 15

438

Arg Leu Asp Thr Asn Lys Ala Thr Leu Leu Thr Ala Ser Gly Glu Leu
 20 25 30

Ile Leu Phe Leu Ile Phe Phe Asn Lys Asp Ile Leu Arg Tyr
 35 40 45

<210> 487

<211> 162

<212> PRT

<213> Homo sapiens

<400> 487

Leu Gly Val Ala Leu Gly Ala Val Pro Lys Leu His Leu Gly Val Leu
 1 5 10 15

Val Ser Thr Gly Leu Arg Thr Ala Val Gly Ser Pro Arg Leu Pro Pro
 20 25 30

Thr Ala Leu Gly Ala Ala Tyr Gly Thr Ala Lys Ser Gly Thr Gly Ile
 35 40 45

Ala Ala Met Ser Val Met Arg Pro Glu Gln Ile Met Lys Ser Ile Ile
 50 55 60

Pro Val Val Met Ala Gly Ile Ile Ala Ile Tyr Gly Leu Val Val Ala
 65 70 75 80

Val Leu Ile Ala Asn Ser Leu Asn Asp Asp Ile Ser Leu Tyr Lys Ser
 85 90 95

Phe Leu Gln Leu Gly Ala Gly Leu Ser Val Gly Leu Ser Gly Leu Ala
 100 105 110

Ala Gly Phe Ala Ile Gly Ile Val Gly Asp Ala Gly Val Arg Gly Thr
 115 120 125

Ala Gln Gln Pro Arg Leu Phe Val Gly Met Ile Leu Ile Leu Ile Phe
 130 135 140

Ala Glu Val Leu Gly Leu Tyr Gly Leu Ile Val Ala Leu Ile Leu Ser
 145 150 155 160

Thr Lys

<210> 488

<211> 114

439

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (95)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (111)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (113)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 488

Gln	Ala	Leu	Arg	Pro	Gly	Ser	Phe	Arg	Gly	Thr	Gly	Arg	Lys	Arg	Glu
1				5					10					15	

Arg	Glu	Arg	Glu	Arg	Met	Ser	Leu	Ser	Asp	Trp	His	Leu	Ala	Val	Lys
	20						25						30		

Leu	Ala	Asp	Gln	Pro	Leu	Ala	Pro	Lys	Ser	Ile	Leu	Gln	Leu	Pro	Glu
	35					40						45			

Ser	Glu	Leu	Gly	Glu	Tyr	Ser	Leu	Gly	Gly	Tyr	Ser	Ile	Ser	Phe	Leu
	50					55					60				

Lys	Gln	Leu	Ile	Ala	Gly	Lys	Leu	Gln	Glu	Ser	Val	Pro	Asp	Pro	Glu
65					70				75					80	

Leu	Ile	Asp	Leu	Ile	Tyr	Cys	Gly	Arg	Lys	Leu	Lys	Asp	Asp	Xaa	Thr
			85						90					95	

Leu	Thr	Ser	Thr	Val	Phe	Asn	Leu	Ala	Pro	His	Pro	Cys	Ser	Xaa	Glu
			100					105						110	

Xaa Leu

<210> 489

<211> 149

<212> PRT

<213> Homo sapiens

<220>

440

<221> SITE

<222> (121)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (142)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 489

Ser	Thr	His	Ala	Ser	Glu	Asp	Val	Leu	Ala	Ala	Pro	Ser	Gly	Cys	Arg
1				5				10						15	

Ala	Ser	Arg	Pro	Pro	Thr	Ser	Gly	Arg	Glu	Gln	Phe	Trp	Ala	Arg	Gly
			20					25					30		

Leu	Ala	Ala	Ala	Asp	Met	Thr	Lys	Gly	Leu	Val	Leu	Gly	Ile	Tyr	Ser
			35				40					45			

Lys	Asp	Lys	Glu	Asp	Asp	Val	Pro	Gln	Phe	Thr	Ser	Ala	Gly	Glu	Asn
	50					55					60				

Phe	Asp	Lys	Leu	Val	Ser	Gly	Lys	Leu	Arg	Glu	Ile	Leu	Asn	Ile	Ser
65					70					75					80

Gly	Pro	Pro	Leu	Lys	Ala	Gly	Lys	Thr	Arg	Thr	Phe	Tyr	Gly	Leu	His
				85					90					95	

Glu	Asp	Phe	Pro	Ser	Val	Val	Val	Val	Gly	Leu	Gly	Arg	Lys	Ala	Ala
			100						105				110		

Gly	Val	Asp	Asp	Gln	Glu	Asn	Trp	Xaa	Glu	Gly	Lys	Glu	Asn	Ile	Arg
		115					120					125			

Val	Ala	Met	Gln	Arg	Gly	Ala	Gly	Arg	Phe	Gln	Asp	Leu	Xaa	Ile	Ser
		130				135						140			

Ser	Val	Glu	Gly	Gly
145				

<210> 490

<211> 527

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (311)

<223> Xaa equals any of the naturally occurring L-amino acids

441

<400> 490

Arg Arg Arg Ser Arg Gly Leu Ile Pro Gly Arg Ala Pro Gly Arg Arg
 1 5 10 15

Arg Pro Arg Ala His Glu Val Ala Arg Ala Pro Pro Pro Ile Ala Met
 20 25 30

Asp Arg Met Lys Lys Ile Lys Arg Gln Leu Ser Met Thr Leu Arg Gly
 35 40 45

Gly Arg Gly Ile Asp Lys Thr Asn Gly Ala Pro Glu Gln Ile Gly Leu
 50 55 60

Asp Glu Ser Gly Gly Gly Gly Gly Ser Asp Pro Gly Glu Ala Pro Thr
 65 70 75 80

Arg Ala Ala Pro Gly Glu Leu Arg Ser Ala Arg Gly Pro Leu Ser Ser
 85 90 95

Ala Pro Glu Ile Val His Glu Asp Leu Lys Met Gly Ser Asp Gly Glu
 100 105 110

Ser Asp Gln Ala Ser Ala Thr Ser Ser Asp Glu Val Gln Ser Pro Val
 115 120 125

Arg Val Arg Met Arg Asn His Pro Pro Arg Lys Ile Ser Thr Glu Asp
 130 135 140

Ile Asn Lys Arg Leu Ser Leu Pro Ala Asp Ile Arg Leu Pro Glu Gly
 145 150 155 160

Tyr Leu Glu Lys Leu Thr Leu Asn Ser Pro Ile Phe Asp Lys Pro Leu
 165 170 175

Ser Arg Arg Leu Arg Arg Val Ser Leu Ser Glu Ile Gly Phe Gly Lys
 180 185 190

Leu Glu Thr Tyr Ile Lys Leu Asp Lys Leu Gly Glu Gly Thr Tyr Ala
 195 200 205

Thr Val Tyr Lys Gly Lys Ser Lys Leu Thr Asp Asn Leu Val Ala Leu
 210 215 220

Lys Glu Ile Arg Leu Glu His Glu Glu Gly Ala Pro Cys Thr Ala Ile
 225 230 235 240

Arg Glu Val Ser Leu Leu Lys Asp Leu Lys His Ala Asn Ile Val Thr
 245 250 255

Leu His Asp Ile Ile His Thr Glu Lys Ser Leu Thr Leu Val Phe Glu

442

260	265	270
Tyr Leu Asp Lys Asp Leu Lys Gln Tyr Leu Asp Asp Cys Gly Asn Ile		
275	280	285
Ile Asn Met His Asn Val Lys Leu Phe Leu Phe Gln Leu Leu Arg Gly		
290	295	300
Leu Ala Tyr Cys His Arg Xaa Lys Val Leu His Arg Asp Leu Lys Pro		
305	310	315 320
Gln Asn Leu Leu Ile Asn Glu Arg Gly Glu Leu Lys Leu Ala Asp Phe		
	325	330 335
Gly Leu Ala Arg Ala Lys Ser Ile Pro Thr Lys Thr Tyr Ser Asn Glu		
	340	345 350
Val Val Thr Leu Trp Tyr Arg Pro Pro Asp Ile Leu Leu Gly Ser Thr		
	355	360 365
Asp Tyr Ser Thr Gln Ile Asp Met Trp Gly Val Gly Cys Ile Phe Tyr		
	370	375 380
Glu Met Ala Thr Gly Arg Pro Leu Phe Pro Gly Ser Thr Val Glu Glu		
	385	390 395 400
Gln Leu His Phe Ile Phe Arg Ile Leu Gly Thr Pro Thr Glu Glu Thr		
	405	410 415
Trp Pro Gly Ile Leu Ser Asn Glu Glu Phe Lys Thr Tyr Asn Tyr Pro		
	420	425 430
Lys Tyr Arg Ala Glu Ala Leu Leu Ser His Ala Pro Arg Leu Asp Ser		
	435	440 445
Asp Gly Ala Asp Leu Leu Thr Lys Leu Leu Gln Phe Glu Gly Arg Asn		
	450	455 460
Arg Ile Ser Ala Glu Asp Ala Met Lys His Pro Phe Phe Leu Ser Leu		
	465	470 475 480
Gly Glu Arg Ile His Lys Leu Pro Asp Thr Thr Ser Ile Phe Ala Leu		
	485	490 495
Lys Glu Ile Gln Leu Gln Lys Glu Ala Ser Leu Arg Ser Ser Ser Met		
	500	505 510
Pro Asp Ser Gly Arg Pro Ala Phe Arg Val Val Asp Thr Glu Phe		
	515	520 525

443

<210> 491
 <211> 125
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (125)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 491
 Cys Thr Arg Ala His Pro Lys Asn Leu Val Glu Lys Gly Ile Leu Thr
 1 5 10 15
 Thr Glu Lys Gln Asn Phe Leu Leu Phe Asp Met Thr Thr His Pro Val
 20 25 30
 Thr Asn Thr Thr Glu Lys Gln Arg Leu Val Lys Lys Leu Gln Asp Ser
 35 40 45
 Val Leu Glu Arg Trp Val Asn Asp Pro Gln Arg Met Asp Lys Arg Thr
 50 55 60
 Leu Ala Leu Leu Val Leu Ala His Ser Ser Asp Val Leu Glu Asn Val
 65 70 75 80
 Phe Ser Ser Leu Thr Asp Asp Lys Tyr Asp Val Ala Met Asn Arg Ala
 85 90 95
 Lys Asp Leu Val Glu Leu Asp Pro Glu Val Glu Gly Thr Lys Pro Ser
 100 105 110
 Ala Thr Glu Met Ile Trp Ala Val Leu Ala Ala Phe Xaa
 115 120 125

<210> 492
 <211> 53
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (3)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (49)

444

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (51)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 492

Val	Ser	Xaa	Ser	Ile	Leu	Ala	Leu	Leu	Phe	Asn	Thr	Asp	Ala	Leu	Phe
1				5					10					15	

Ser	Arg	Val	Tyr	Glu	Ser	Leu	Ser	Asp	Asn	His	Gly	Leu	Gln	Glu	Gln
			20					25					30		

Thr	Val	Glu	Lys	Leu	Phe	Phe	Gln	Trp	Lys	Ser	Trp	Val	Gln	Glu	Met
			35				40					45			

Xaa	Gly	Xaa	Leu	Lys
				50

<210> 493

<211> 82

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (60)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (67)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (68)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (79)

<223> Xaa equals any of the naturally occurring L-amino acids

.445

<400> 493

Pro Gly Phe Phe Phe Gln Met Leu Val His Thr Tyr Ser Ser Met Asp
 1 5 10 15

Arg His Asp Gly Val Pro Ser His Ser Ser Arg Leu Ser Gln Leu Gly
 20 25 30

Ser Val Ser Gln Gly Pro Tyr Ser Ser Ala Pro Pro Leu Ser His Thr
 35 40 45

Pro Ser Ser Asp Phe Gln Pro Pro Tyr Phe Pro Xaa Pro Tyr Gln Pro
 50 55 60

Leu Pro Xaa Xaa Gln Ser Gln Asp Pro Tyr Ser His Val Xaa Xaa Pro
 65 70 75 80

Tyr Pro

<210> 494

<211> 290

<212> PRT

<213> Homo sapiens

<400> 494

Tyr Lys Asp Trp Leu Thr Lys Met Ser Gly Lys His Asp Val Gly Ala
 1 5 10 15

Tyr Met Leu Met Tyr Lys Gly Ala Asn Arg Thr Glu Thr Val Thr Ser
 20 25 30

Phe Arg Lys Arg Glu Ser Lys Val Pro Ala Asp Leu Leu Lys Arg Ala
 35 40 45

Phe Val Arg Met Ser Thr Ser Pro Glu Ala Phe Leu Ala Leu Arg Ser
 50 55 60

His Phe Ala Ser Ser His Ala Leu Ile Cys Ile Ser His Trp Ile Leu
 65 70 75 80

Gly Ile Gly Asp Arg His Leu Asn Asn Phe Met Val Ala Met Glu Thr
 85 90 95

Gly Gly Val Ile Gly Ile Asp Phe Gly His Ala Phe Gly Ser Ala Thr
 100 105 110

Gln Phe Leu Pro Val Pro Glu Leu Met Pro Phe Arg Leu Thr Arg Gln
 115 120 125

446

Phe Ile Asn Leu Met Leu Pro Met Lys Glu Thr Gly Leu Met Tyr Ser
 130 135 140
 Ile Met Val His Ala Leu Arg Ala Phe Arg Ser Asp Pro Gly Leu Leu
 145 150 155 160
 Thr Asn Thr Met Asp Val Phe Val Lys Glu Pro Ser Phe Asp Trp Lys
 165 170 175
 Asn Phe Glu Gln Lys Met Leu Lys Lys Gly Gly Ser Trp Ile Gln Glu
 180 185 190
 Ile Asn Val Ala Glu Lys Asn Trp Tyr Pro Arg Gln Lys Ile Cys Tyr
 195 200 205
 Ala Lys Arg Lys Leu Ala Gly Ala Asn Pro Ala Val Ile Thr Cys Asp
 210 215 220
 Glu Leu Leu Leu Gly His Glu Lys Ala Pro Ala Phe Arg Asp Tyr Val
 225 230 235 240
 Ala Val Ala Arg Gly Ser Lys Asp His Asn Ile Arg Ala Gln Glu Pro
 245 250 255
 Glu Ser Gly Leu Ser Glu Glu Thr Gln Val Lys Cys Leu Met Asp Gln
 260 265 270
 Ala Thr Asp Pro Asn Ile Leu Gly Arg Thr Trp Glu Gly Trp Glu Pro
 275 280 285
 Trp Met
 290

<210> 495

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (148)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 495

Cys Gln Ser His Pro Leu Pro Gly Gly Pro Ala Cys Pro Cys Leu Ala
 1 5 10 15

Cys His Ile Thr Leu Leu Phe Gly Arg Pro Trp Leu Ile Lys Glu Val

447

20 25 30
 Leu Val Val Ser Gln Ala Lys Trp Asn Leu Glu Thr Val Lys Lys Val
 35 40 45
 Gln Ile Thr Leu Asn Cys Ile Gln Glu Val His Phe Phe Pro Ile Val
 50 55 60
 Arg Gly Ser Trp Ser Leu Arg Asp Ala Arg Leu Glu Ser Asp Tyr Ile
 65 70 75 80
 Ile Ile Gln Asn Gly Asn Ser Gln Gly Asn Ala Phe Phe His Phe Ile
 85 90 95
 Arg Phe Phe Tyr Pro His Cys Thr Pro Ser Pro Ser Pro Leu Pro Ile
 100 105 110
 Trp Met Ala Ser Gln Lys Leu Gly Pro Ser Pro Pro Cys Leu Gly Gly
 115 120 125
 Gly Gln Ser Pro Leu Thr Ala Glu Ala Ala Leu Leu Ser Ser Ala Val
 130 135 140
 Leu Pro Leu Xaa Lys Cys Leu Gln Arg Val Met Ser
 145 150 155

<210> 496

<211> 251

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (42)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 496

Glu Glu Leu Leu Arg Ala Gln Glu Ala Pro Gly Gln Ala Glu Pro Pro
 1 5 10 15
 Ala Ala Ala Glu Val Gln Gly Ala Gly Asn Glu Asn Glu Pro Arg Glu
 20 25 30
 Ala Asp Lys Ser His Pro Glu Gln Arg Xaa Leu Arg Pro Arg Leu Cys
 35 40 45
 Thr Met Lys Lys Gly Pro Ser Gly Tyr Gly Phe Asn Leu His Ser Asp
 50 55 60

448

Lys Ser Lys Pro Gly Gln Phe Ile Arg Ser Val Asp Pro Asp Ser Pro
 65 70 75 80
 Ala Glu Ala Ser Gly Leu Arg Ala Gln Asp Arg Ile Val Glu Val Asn
 85 90 95
 Gly Val Cys Met Glu Gly Lys Gln His Gly Asp Val Val Ser Ala Ile
 100 105 110
 Arg Ala Gly Gly Asp Glu Thr Lys Leu Leu Val Val Asp Arg Glu Thr
 115 120 125
 Asp Glu Phe Phe Lys Lys Cys Arg Val Ile Pro Ser Gln Glu His Leu
 130 135 140
 Asn Gly Pro Leu Pro Val Pro Phe Thr Asn Gly Glu Ile Gln Lys Glu
 145 150 155 160
 Asn Ser Arg Glu Ala Leu Ala Glu Ala Ala Leu Glu Ser Pro Arg Pro
 165 170 175
 Ala Leu Val Arg Ser Ala Ser Ser Asp Thr Ser Glu Glu Leu Asn Ser
 180 185 190
 Gln Asp Ser Pro Pro Lys Gln Asp Ser Thr Ala Pro Ser Ser Thr Ser
 195 200 205
 Ser Ser Asp Pro Ile Leu Asp Phe Asn Ile Ser Leu Ala Met Ala Lys
 210 215 220
 Glu Arg Ala His Gln Lys Arg Ser Ser Lys Arg Ala Pro Gln Met Asp
 225 230 235 240
 Trp Ser Lys Lys Asn Glu Leu Phe Ser Asn Leu
 245 250

<210> 497

<211> 48

<212> PRT

<213> Homo sapiens

<400> 497

Asn Gly Ala Glu Ala Val Ser Thr Glu Ala Lys Met Thr Ala Phe Pro
 1 5 10 15
 Asp Trp Pro Trp Leu Phe His Thr Leu Cys Asp Pro Cys Pro Met Thr
 20 25 30
 Leu Trp Leu Thr Leu Pro Glu Ala Met Thr Thr Ala Ala Phe Cys His

449

35

40

45

<210> 498

<211> 373

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (337)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (372)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 498

Gly Thr Arg Gly Ser Arg Ala Ser Gly Val Cys Ala Arg Gly Cys Leu
 1 5 10 15

Asp Ser Ala Gly Pro Trp Thr Met Ser Arg Ala Leu Arg Pro Pro Leu
 20 25 30

Pro Pro Leu Cys Phe Phe Leu Leu Leu Leu Ala Ala Ala Gly Ala Arg
 35 40 45

Ala Gly Gly Tyr Glu Thr Cys Pro Thr Val Gln Pro Asn Met Leu Asn
 50 55 60

Val His Leu Leu Pro His Thr His Asp Asp Val Gly Trp Leu Lys Thr
 65 70 75 80

Val Asp Gln Tyr Phe Tyr Gly Ile Lys Asn Asp Ile Gln His Ala Gly
 85 90 95

Val Gln Tyr Ile Leu Asp Ser Val Ile Ser Ala Leu Leu Ala Asp Pro
 100 105 110

Thr Arg Arg Phe Ile Tyr Val Glu Ile Ala Phe Phe Ser Arg Trp Trp
 115 120 125

His Gln Gln Thr Asn Ala Thr Gln Glu Val Val Arg Asp Leu Val Arg
 130 135 140

Gln Gly Arg Leu Glu Phe Ala Asn Gly Gly Trp Val Met Asn Asp Glu

450

145		150		155		160
Ala Ala Thr His Tyr Gly Ala Ile Val Asp Gln Met Thr Leu Gly Leu						
	165		170		175	
Arg Phe Leu Glu Asp Thr Phe Gly Asn Asp Gly Arg Pro Arg Val Ala						
	180		185		190	
Trp His Ile Asp Pro Phe Gly His Ser Arg Glu Gln Ala Ser Leu Phe						
	195		200		205	
Ala Gln Met Gly Phe Asp Gly Phe Phe Phe Gly Arg Leu Asp Tyr Gln						
	210		215		220	
Asp Lys Trp Val Arg Met Gln Lys Leu Glu Met Glu Gln Val Trp Arg						
	225		230		235	240
Ala Ser Thr Ser Leu Lys Pro Pro Thr Ala Asp Leu Phe Thr Gly Val						
	245		250		255	
Leu Pro Asn Gly Tyr Asn Pro Pro Arg Asn Leu Cys Trp Asp Val Leu						
	260		265		270	
Cys Val Asp Gln Pro Leu Val Glu Asp Pro Arg Ser Pro Glu Tyr Asn						
	275		280		285	
Ala Lys Glu Leu Val Asp Tyr Phe Leu Asn Val Ala Thr Ala Gln Gly						
	290		295		300	
Arg Tyr Tyr Arg Thr Asn His Thr Val Met Thr Met Gly Ser Asp Phe						
	305		310		315	320
Gln Tyr Glu Asn Ala Asn Met Trp Phe Lys Asn Leu Asp Lys Leu Ile						
	325		330		335	
Xaa Leu Val Asn Ala Gln Gly Lys Arg Lys Gln Cys Pro Cys Ser Leu						
	340		345		350	
Leu His Pro Arg Leu Leu Pro Leu Gly Ala Glu Gln Gly Gln Pro His						
	355		360		365	
Leu Val Ser Xaa Thr						
	370					

<210> 499

<211> 238

<212> PRT

<213> Homo sapiens

451

<400> 499

Ala Leu Pro Gly Pro Asp Trp His Gly Ala Gly Ala Ala Asp Arg Gly
 1 5 10 15
 Pro Ala Ala Pro Pro Arg Pro Gly Pro Cys Ala Tyr Ala Ala His Gly
 20 25 30
 Arg Gly Ala Leu Ala Glu Ala Ala Arg Arg Cys Leu His Asp Ile Ala
 35 40 45
 Leu Ala His Arg Ala Ala Thr Ala Ala Arg Pro Pro Ala Pro Pro Pro
 50 55 60
 Ala Pro Gln Pro Pro Ser Pro Thr Pro Ser Pro Pro Arg Pro Thr Leu
 65 70 75 80
 Ala Arg Glu Asp Asn Glu Glu Asp Glu Asp Glu Pro Thr Glu Thr Glu
 85 90 95
 Thr Ser Gly Glu Gln Leu Gly Ile Ser Asp Asn Gly Gly Leu Phe Val
 100 105 110
 Met Asp Glu Asp Ala Thr Leu Gln Asp Leu Pro Pro Phe Cys Glu Ser
 115 120 125
 Asp Pro Glu Ser Thr Asp Asp Gly Ser Leu Ser Glu Glu Thr Pro Ala
 130 135 140
 Gly Pro Pro Thr Cys Ser Val Pro Pro Ala Ser Ala Leu Pro Thr Gln
 145 150 155 160
 Gln Tyr Ala Lys Ser Leu Pro Val Ser Val Pro Val Trp Gly Phe Lys
 165 170 175
 Glu Lys Arg Thr Glu Ala Arg Ser Ser Asp Glu Glu Asn Gly Pro Pro
 180 185 190
 Ser Ser Pro Asp Leu Asp Arg Ile Ala Ala Ser Met Arg Ala Leu Val
 195 200 205
 Leu Arg Glu Ala Glu Asp Thr Gln Val Phe Gly Asp Leu Pro Arg Pro
 210 215 220
 Arg Leu Asn Thr Ser Asp Phe Gln Lys Leu Lys Arg Lys Tyr
 225 230 235

<210> 500

<211> 198

<212> PRT

452

<213> Homo sapiens

<220>

<221> SITE

<222> (94)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (156)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 500

Asn	Ser	Ala	Glu	Leu	Ser	Pro	Gly	Leu	Cys	Ser	Pro	Thr	Pro	Thr	Glu
1				5					10					15	

Ala	Arg	Ala	Gly	Asp	Ala	Gly	Pro	Ala	Ala	Arg	Ser	Arg	Lys	Gln	Asn
			20					25					30		

Pro	Gln	Ser	Pro	Pro	Cys	Cys	Cys	Val	Asp	Asp	Thr	Trp	Ala	Gln	Ala
	35						40					45			

Glu	Val	Gly	Pro	Val	Thr	Ser	Cys	Thr	Gly	Phe	Val	Glu	Gly	Ser	Ser
	50					55					60				

Arg	Thr	Gly	Gly	Met	Gly	Ser	Ala	Cys	Ile	Lys	Val	Thr	Lys	Tyr	Phe
65					70					75					80

Leu	Phe	Leu	Phe	Asn	Leu	Ile	Phe	Phe	Ile	Leu	Gly	Ala	Xaa	Ile	Leu
				85					90					95	

Gly	Phe	Gly	Val	Trp	Ile	Leu	Ala	Asp	Lys	Ser	Ser	Phe	Ile	Ser	Val
			100					105					110		

Leu	Gln	Thr	Ser	Ser	Ser	Ser	Leu	Arg	Met	Gly	Ala	Tyr	Val	Phe	Ile
		115					120					125			

Gly	Val	Gly	Ala	Val	Thr	Met	Leu	Met	Gly	Phe	Leu	Gly	Cys	Ile	Gly
	130					135					140				

Ala	Val	Asn	Glu	Val	Arg	Cys	Leu	Leu	Gly	Leu	Xaa	Phe	Ala	Phe	Leu
145					150					155					160

Leu	Leu	Ile	Leu	Ile	Ala	Gln	Val	Thr	Ala	Gly	Ala	Leu	Phe	Tyr	Phe
			165						170					175	

Asn	Met	Gly	Lys	Val	Ser	Pro	Ser	Leu	Pro	Pro	Ser	Ser	Leu	Gly	Trp
			180					185					190		

Thr	Asn	His	Gly	Gly	Asp
			195		

453

<210> 501

<211> 169

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (165)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 501

Ser Ser Ala Ser Thr Asn Met Ser Arg Gly Ser Ser Ala Gly Phe Asp
 1 5 10 15

Arg His Ile Thr Ile Phe Ser Pro Glu Gly Arg Leu Tyr Gln Val Glu
 20 25 30

Tyr Ala Phe Lys Ala Ile Asn Gln Gly Gly Leu Thr Ser Val Ala Val
 35 40 45

Arg Gly Lys Asp Cys Ala Val Ile Val Thr Gln Lys Lys Val Pro Asp
 50 55 60

Lys Leu Leu Asp Ser Ser Thr Val Thr His Leu Phe Lys Ile Thr Glu
 65 70 75 80

Asn Ile Gly Cys Val Met Thr Gly Met Thr Ala Asp Ser Arg Ser Gln
 85 90 95

Val Gln Arg Ala Arg Tyr Glu Ala Ala Asn Trp Lys Tyr Lys Tyr Gly
 100 105 110

Tyr Glu Ile Pro Val Asp Met Leu Cys Lys Arg Ile Ala Asp Ile Ser
 115 120 125

Gln Val Tyr Thr Gln Asn Ala Glu Met Arg Pro Leu Gly Cys Cys Met
 130 135 140

Ile Leu Ile Gly Ile Asp Glu Glu Gln Gly Pro Gln Val Tyr Lys Cys
 145 150 155 160

Asp Pro Ala Gly Xaa Tyr Cys Gly Val
 165

<210> 502

<211> 507

454

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (361)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (461)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 502

Val	Arg	Gln	Leu	Cys	Arg	Pro	Ala	Glu	Xaa	Asp	Ser	Val	Met	Ala	Glu
1				5					10					15	

Gln	Val	Ala	Leu	Ser	Arg	Thr	Gln	Val	Cys	Gly	Ile	Leu	Arg	Glu	Glu
			20					25					30		

Leu	Phe	Gln	Gly	Asp	Ala	Phe	His	Gln	Ser	Asp	Thr	His	Ile	Phe	Ile
	35						40					45			

Ile	Met	Gly	Ala	Ser	Gly	Asp	Leu	Ala	Lys	Lys	Lys	Ile	Tyr	Pro	Thr
	50					55					60				

Ile	Trp	Trp	Leu	Phe	Arg	Asp	Gly	Leu	Leu	Pro	Glu	Asn	Thr	Phe	Ile
65					70					75					80

Val	Gly	Tyr	Ala	Arg	Ser	Arg	Leu	Thr	Val	Ala	Asp	Ile	Arg	Lys	Gln
				85					90					95	

Ser	Glu	Pro	Phe	Phe	Lys	Ala	Thr	Pro	Glu	Glu	Lys	Leu	Lys	Leu	Glu
			100					105					110		

Asp	Phe	Phe	Ala	Arg	Asn	Ser	Tyr	Val	Ala	Gly	Gln	Tyr	Asp	Asp	Ala
	115						120					125			

Ala	Ser	Tyr	Gln	Arg	Leu	Asn	Ser	His	Met	Asn	Ala	Leu	His	Leu	Gly
	130					135					140				

Ser	Gln	Ala	Asn	Arg	Leu	Phe	Tyr	Leu	Ala	Leu	Pro	Pro	Thr	Val	Tyr
145					150					155					160

Glu	Ala	Val	Thr	Lys	Asn	Ile	His	Glu	Ser	Cys	Met	Ser	Gln	Ile	Gly
				165					170					175	

455

Trp Asn Arg Ile Ile Val Glu Lys Pro Phe Gly Arg Asp Leu Gln Ser
 180 185 190
 Ser Asp Arg Leu Ser Asn His Ile Ser Ser Leu Phe Arg Glu Asp Gln
 195 200 205
 Ile Tyr Arg Ile Asp His Tyr Leu Gly Lys Glu Met Val Gln Asn Leu
 210 215 220
 Met Val Leu Arg Phe Ala Asn Arg Ile Phe Gly Pro Ile Trp Asn Arg
 225 230 235 240
 Asp Asn Ile Ala Cys Val Ile Leu Thr Phe Lys Glu Pro Phe Gly Thr
 245 250 255
 Glu Gly Arg Gly Gly Tyr Phe Asp Glu Phe Gly Ile Ile Arg Asp Val
 260 265 270
 Met Gln Asn His Leu Leu Gln Met Leu Cys Leu Val Ala Met Glu Lys
 275 280 285
 Pro Ala Ser Thr Asn Ser Asp Asp Val Arg Asp Glu Lys Val Lys Val
 290 295 300
 Leu Lys Cys Ile Ser Glu Val Gln Ala Asn Asn Val Val Leu Gly Gln
 305 310 315 320
 Tyr Val Gly Asn Pro Asp Gly Glu Gly Glu Ala Thr Lys Gly Tyr Leu
 325 330 335
 Asp Asp Pro Thr Val Pro Arg Gly Ser Thr Thr Ala Thr Phe Ala Ala
 340 345 350
 Val Val Leu Tyr Val Glu Asn Glu Xaa Trp Asp Gly Val Pro Phe Ile
 355 360 365
 Leu Arg Cys Gly Lys Ala Leu Asn Glu Arg Lys Ala Glu Val Arg Leu
 370 375 380
 Gln Phe His Asp Val Ala Gly Asp Ile Phe His Gln Gln Cys Lys Arg
 385 390 395 400
 Asn Glu Leu Val Ile Arg Val Gln Pro Asn Glu Ala Val Tyr Thr Lys
 405 410 415
 Met Met Thr Lys Lys Pro Gly Met Phe Phe Asn Pro Glu Glu Ser Glu
 420 425 430
 Leu Asp Leu Thr Tyr Gly Asn Arg Tyr Lys Asn Val Lys Leu Pro Asp
 435 440 445

456

Ala Tyr Glu Arg Leu Ile Leu Asp Val Phe Cys Gly Xaa Gln Met His
 450 455 460

Phe Val Arg Arg Thr Ser Ser Val Arg Pro Gly Val Phe Ser Pro His
 465 470 475 480

Cys Cys Thr Arg Leu Ser Trp Arg Ser Pro Ser Pro Ser Pro Ile Phe
 485 490 495

Met Ala Ala Glu Ala Pro Arg Arg Gln Thr Ser
 500 505

<210> 503

<211> 260

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (69)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 503

Gly Pro Glu Val Leu Pro Glu Pro Arg Val Pro Arg Glu Ala Leu Ala
 1 5 10 15

Phe Ile Ile Arg Ser Phe Gly Gly Glu Val Ser Trp Asp Lys Ser Leu
 20 25 30

Cys Ile Gly Ala Thr Tyr Asp Val Thr Asp Ser Arg Ile Thr His Gln
 35 40 45

Ile Val Asp Arg Pro Gly Gln Gln Thr Ser Val Ile Gly Arg Cys Tyr
 50 55 60

Val Gln Pro Gln Xaa Val Phe Asp Ser Val Asn Ala Arg Leu Leu Leu
 65 70 75 80

Pro Val Ala Glu Tyr Phe Ser Gly Val Gln Leu Pro Pro His Leu Ser
 85 90 95

Pro Phe Val Thr Glu Lys Glu Gly Asp Tyr Val Pro Pro Glu Lys Leu
 100 105 110

Lys Leu Leu Ala Leu Gln Arg Gly Glu Asp Pro Gly Asn Leu Asn Glu
 115 120 125

Ser Glu Glu Glu Glu Glu Asp Asp Asn Asn Glu Gly Asp Gly Asp

457

130	135	140
Glu Glu Gly Glu Asn Glu Glu Glu Glu Glu Asp Ala Glu Ala Gly Ser		
145	150	155 160
Glu Lys Glu Glu Glu Ala Arg Leu Ala Ala Leu Glu Glu Gln Arg Met		
165	170	175
Glu Gly Lys Lys Pro Arg Val Met Ala Gly Thr Leu Lys Leu Glu Asp		
180	185	190
Lys Gln Arg Leu Ala Gln Glu Glu Glu Ser Glu Ala Lys Arg Leu Ala		
195	200	205
Ile Met Met Met Lys Lys Arg Glu Lys Tyr Leu Tyr Gln Lys Ile Met		
210	215	220
Phe Gly Lys Arg Arg Lys Ile Arg Glu Ala Asn Lys Leu Ala Glu Lys		
225	230	235 240
Arg Lys Ala His Asp Glu Ala Val Arg Ser Glu Lys Lys Ala Lys Lys		
245	250	255
Ala Arg Pro Glu		
260		

<210> 504

<211> 424

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (292)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (342)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 504

Leu Leu Gln Arg Cys Tyr Ala Phe Pro Gly His Arg Leu Ala His Ser
1 5 10 15

Gly Ser Asp Leu Ser Leu Leu Val Pro Glu Ile Glu Asp Met Tyr Ser
20 25 30

Ser Pro Tyr Leu Arg Pro Ser Glu Ser Pro Ile Thr Val Glu Val Asn

458

35	40	45
Cys Thr Asn Pro Gly Thr Arg Tyr Cys Trp Met Ser Thr Gly Leu Tyr		
50	55	60
Ile Pro Gly Arg Gln Ile Ile Glu Val Ser Leu Pro Glu Ala Ala Ala		
65	70	75
Ser Ala Asp Leu Lys Ile Gln Ile Gly Cys His Thr Asp Asp Leu Thr		
85	90	95
Arg Ala Ser Lys Leu Phe Arg Gly Pro Leu Val Ile Asn Arg Cys Cys		
100	105	110
Leu Asp Lys Pro Thr Lys Ser Ile Thr Cys Leu Trp Gly Gly Leu Leu		
115	120	125
Tyr Ile Ile Val Pro Gln Asn Ser Lys Leu Gly Ser Val Pro Val Thr		
130	135	140
Val Lys Gly Ala Val His Ala Pro Tyr Tyr Lys Leu Gly Glu Thr Thr		
145	150	155
Leu Glu Glu Trp Lys Arg Arg Ile Gln Glu Asn Pro Gly Pro Trp Gly		
165	170	175
Glu Leu Ala Thr Asp Asn Ile Ile Leu Thr Val Pro Thr Ala Asn Leu		
180	185	190
Arg Thr Leu Glu Asn Pro Glu Pro Leu Leu Arg Leu Trp Asp Glu Val		
195	200	205
Met Gln Ala Val Ala Arg Leu Gly Ala Glu Pro Phe Pro Leu Arg Leu		
210	215	220
Pro Gln Arg Ile Val Ala Asp Val Gln Ile Ser Val Gly Trp Met His		
225	230	235
Ala Gly Tyr Pro Ile Met Cys His Leu Glu Ser Val Gln Glu Leu Ile		
245	250	255
Asn Glu Lys Leu Ile Arg Thr Lys Gly Leu Trp Gly Pro Val His Glu		
260	265	270
Leu Gly Arg Asn Gln Gln Arg Gln Glu Trp Glu Phe Pro Pro His Thr		
275	280	285
Thr Glu Ala Xaa Cys Asn Leu Trp Cys Val Tyr Val His Glu Thr Val		
290	295	300
Leu Gly Ile Pro Arg Ser Arg Ala Asn Ile Ala Leu Trp Pro Pro Val		

459

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305              310              315              320
Arg Glu Lys Arg Val Arg Ile Tyr Leu Ser Lys Gly Pro Asn Val Lys
      325              330              335
Asn Trp Asn Ala Trp Xaa Ala Leu Glu Thr Tyr Leu Gln Leu Gln Glu
      340              345              350
Ala Phe Gly Trp Glu Pro Phe Ile Arg Leu Phe Thr Glu Tyr Arg Asn
      355              360              365
Gln Thr Asn Leu Pro Thr Glu Asn Val Asp Lys Met Asn Leu Trp Val
      370              375              380
Lys Met Phe Ser His Gln Val Gln Lys Asn Leu Ala Pro Phe Phe Glu
385              390              395              400
Ala Trp Ala Gly Pro Ser Arg Arg Lys Trp Leu Pro Ala Trp Pro Ile
      405              410              415
Cys Leu Asn Gly Arg Lys Ile Leu
      420

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<210> 505

<211> 70

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (54)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (66)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (70)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 505

460

Leu His Gln Ser Leu Leu His Leu Glu Lys Thr Asn Glu Arg Lys Ser
 1 5 10 15
 Ile Phe Leu Ile His Tyr Pro Asn Asn Asn Arg Thr Pro Tyr Arg Asn
 20 25 30
 Tyr Tyr His Tyr Val Ser Lys His Tyr Ile Pro Ile Thr Tyr Pro Thr
 35 40 45
 Xaa Ser Ile Ile Asp Xaa Ile Ser Ile Pro Thr Met Ile Ser Ala Leu
 50 55 60
 Asn Xaa Gln Asn Lys Xaa
 65 70

<210> 506

<211> 434

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (69)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (363)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 506

Ser Thr His Ala Ser Ala His Ala Ser Val Ser Thr Ala Ala Ala Ala
 1 5 10 15
 Ala Leu Ala Ala Ala Val Lys Ala Lys His Leu Ala Ala Val Glu
 20 25 30
 Glu Arg Lys Ile Lys Ser Leu Val Ala Leu Leu Val Glu Thr Gln Met
 35 40 45
 Lys Lys Leu Glu Ile Lys Leu Arg His Phe Glu Glu Leu Glu Thr Ile
 50 55 60
 Met Asp Arg Glu Xaa Glu Ala Leu Glu Tyr Gln Arg Gln Gln Leu Leu

461

65	70	75	80
Ala Asp Arg Gln Ala Phe His Met Glu Gln Leu Lys Tyr Ala Glu Met	85	90	95
Arg Ala Arg Gln Gln His Phe Gln Gln Met His Gln Gln Gln Gln Gln	100	105	110
Pro Pro Pro Ala Leu Pro Pro Gly Ser Gln Pro Ile Pro Pro Thr Gly	115	120	125
Ala Ala Gly Pro Pro Ala Xaa His Gly Leu Ala Val Ala Pro Ala Ser	130	135	140
Val Val Pro Ala Pro Ala Gly Ser Gly Ala Pro Pro Gly Ser Leu Gly	145	150	155
Pro Ser Glu Gln Ile Gly Gln Ala Gly Ser Thr Ala Gly Pro Gln Gln	165	170	175
Gln Gln Pro Ala Gly Ala Pro Gln Pro Gly Ala Val Pro Pro Gly Val	180	185	190
Pro Pro Pro Gly Pro His Gly Pro Ser Pro Phe Pro Asn Gln Gln Thr	195	200	205
Pro Pro Ser Met Met Pro Gly Ala Val Pro Gly Ser Gly His Pro Gly	210	215	220
Val Ala Gly Asn Ala Pro Leu Gly Leu Pro Phe Gly Met Pro Pro Pro	225	230	235
Pro Pro Pro Pro Ala Pro Ser Ile Ile Pro Phe Gly Ser Leu Ala Asp	245	250	255
Ser Ile Ser Ile Asn Leu Pro Ala Pro Pro Asn Leu His Gly His His	260	265	270
His His Leu Pro Phe Ala Pro Gly Thr Leu Pro Pro Pro Asn Leu Pro	275	280	285
Val Ser Met Ala Asn Pro Leu His Pro Asn Leu Pro Ala Thr Thr Thr	290	295	300
Met Pro Ser Ser Leu Pro Leu Gly Pro Gly Leu Gly Ser Ala Ala Ala	305	310	315
Gln Ser Pro Ala Ile Val Ala Ala Val Gln Gly Asn Leu Leu Pro Ser	325	330	335
Ala Ser Pro Leu Pro Asp Pro Gly Thr Pro Leu Pro Pro Asp Pro Thr			

462

[illegible]

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<210> 507
<211> 303
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (165)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>  
<221> SITE  
<222> (280)  
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 507

Glu Tyr Val Phe Pro Ala Lys Lys Lys Leu Gln Glu Tyr Arg Val Leu
1 5 10 15

Ile Thr Thr Leu Ile Thr Ala Gly Ser Trp Ser Arg Pro Ser Phe Pro
20 25 30

Leu Ile Thr Ser His Thr Ser Ser Ser Met Arg Leu Ala Thr Ala Trp
35 40 45

Ser Leu Arg Ser Leu Val Ala Ile Ala Gly Leu Met Glu Val Lys Glu
50 55 60

Thr Gly Asp Pro Gly Gly Gln Leu Val Leu Ala Gly Asp Pro Arg Gln

463

65		70		75		80
Leu Gly Pro Val Leu Arg Ser Pro Leu Thr Gln Lys His Gly Leu Gly						
	85		90		95	
Tyr Ser Leu Leu Glu Arg Leu Leu Thr Tyr Asn Ser Leu Tyr Lys Lys						
	100		105		110	
Gly Pro Asp Gly Tyr Asp Pro Gln Phe Ile Thr Lys Leu Leu Arg Asn						
	115		120		125	
Tyr Arg Ser His Pro Thr Ile Leu Asp Ile Pro Asn Gln Leu Tyr Tyr						
	130		135		140	
Glu Gly Glu Leu Gln Ala Cys Ala Asp Val Val Asp Arg Glu Arg Phe						
	145		150		155	160
Cys Arg Trp Ala Xaa Leu Pro Arg Gln Gly Phe Pro Ile Ile Phe His						
	165		170		175	
Gly Val Met Gly Lys Asp Glu Arg Glu Gly Asn Ser Pro Ser Phe Phe						
	180		185		190	
Asn Pro Glu Glu Ala Ala Thr Val Thr Ser Tyr Leu Lys Leu Leu Leu						
	195		200		205	
Ala Pro Ser Ser Lys Lys Gly Lys Ala Arg Leu Ser Pro Arg Ser Val						
	210		215		220	
Gly Val Ile Ser Pro Tyr Arg Lys Gln Val Glu Lys Ile Arg Tyr Cys						
	225		230		235	240
Ile Thr Lys Leu Asp Arg Glu Leu Arg Gly Leu Asp Asp Ile Lys Asp						
	245		250		255	
Leu Lys Val Gly Ser Val Glu Glu Phe Gln Gly Gln Glu Arg Ser Val						
	260		265		270	
Ile Leu Ile Ser Thr Val Arg Xaa Ala Arg Ala Leu Cys Ser Trp Ile						
	275		280		285	
Trp Thr Leu Ile Trp Val Ser Leu Arg Thr Pro Arg Gly Ser Met						
	290		295		300	

<210> 508

<211> 250

<212> PRT

<213> Homo sapiens

464

<220>

<221> SITE

<222> (16)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 508

Glu Gln Tyr Leu Pro Leu Thr Glu Glu Glu Leu Glu Lys Glu Ala Xaa
 1 5 10 15

Lys Val Glu Gly Phe Asp Leu Val Gln Lys Pro Ser Tyr Tyr Val Arg
 20 25 30

Leu Gly Ser Leu Ser Thr Lys Leu His Ser Arg Ala Tyr Gln Gln Ala
 35 40 45

Leu Ser Arg Val Lys Glu Ala Lys Gln Lys Ser Gln Gln Thr Ile Ser
 50 55 60

Gln Leu His Ser Thr Val His Leu Ile Glu Phe Ala Arg Lys Asn Val
 65 70 75 80

Tyr Ser Ala Asn Gln Lys Ile Gln Asp Ala Gln Asp Lys Leu Tyr Leu
 85 90 95

Ser Trp Val Glu Trp Lys Arg Ser Ile Gly Tyr Asp Asp Thr Asp Glu
 100 105 110

Ser His Cys Ala Glu His Ile Glu Ser Arg Thr Leu Ala Ile Ala Arg
 115 120 125

Asn Leu Thr Gln Gln Leu Gln Thr Thr Cys His Thr Leu Leu Ser Asn
 130 135 140

Ile Gln Gly Val Pro Gln Asn Ile Gln Asp Gln Ala Lys His Met Gly
 145 150 155 160

Val Met Ala Gly Asp Ile Tyr Ser Val Phe Arg Asn Ala Ala Ser Phe
 165 170 175

Lys Glu Val Ser Asp Ser Leu Leu Thr Ser Ser Lys Gly Gln Leu Gln
 180 185 190

Lys Met Lys Glu Ser Leu Asp Asp Val Met Asp Tyr Leu Val Asn Asn
 195 200 205

Thr Pro Leu Asn Trp Leu Val Gly Pro Phe Tyr Pro Gln Leu Thr Glu
 210 215 220

Ser Gln Asn Ala Gln Asp Gln Gly Ala Glu Met Asp Lys Ser Ser Gln
 225 230 235 240

465

Glu Thr Gln Arg Ser Glu His Lys Thr His
 245 250

<210> 509

<211> 98

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (97)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 509

His Glu Leu Trp Gly Cys Gly Pro Val Thr Pro Arg Arg Thr Ala Pro
 1 5 10 15

Ser Gly Trp Ala Gln Ala Pro Leu Ser Asp Thr Ala Gln Val Tyr Met
 20 25 30

Glu Leu Gln Gly Leu Val Asp Pro Gln Ile Gln Leu Pro Leu Leu Ala
 35 40 45

Ala Arg Ser Thr Ser Cys Arg Ser Ser Leu Ile Ala Ser Gln Pro Gly
 50 55 60

Pro His Gln Lys Gly Arg Gln Gly Leu Arg Gly Asn Lys Ser Phe Leu
 65 70 75 80

Pro Ser Ser Trp Asn Cys Gln Asn Trp Thr Arg Gln Pro Leu Thr Ser
 85 90 95

Xaa Ser

<210> 510

<211> 392

<212> PRT

<213> Homo sapiens

<400> 510

Gly Ala Met Arg Gly Asp Arg Gly Arg Gly Arg Gly Arg Phe Gly
 1 5 10 15

Ser Arg Gly Gly Pro Gly Gly Gly Phe Arg Pro Phe Val Pro His Ile
 20 25 30

466

Pro Phe Asp Phe Tyr Leu Cys Glu Met Ala Phe Pro Arg Val Lys Pro
 35 40 45
 Ala Pro Asp Glu Thr Ser Phe Ser Glu Ala Leu Leu Lys Arg Asn Gln
 50 55 60
 Asp Leu Ala Pro Asn Ser Ala Glu Gln Ala Ser Ile Leu Ser Leu Val
 65 70 75 80
 Thr Lys Ile Asn Asn Val Ile Asp Asn Leu Ile Val Ala Pro Gly Thr
 85 90 95
 Phe Glu Val Gln Ile Glu Glu Val Arg Gln Val Gly Ser Tyr Lys Lys
 100 105 110
 Gly Thr Met Thr Thr Gly His Asn Val Ala Asp Leu Val Val Ile Leu
 115 120 125
 Lys Ile Leu Pro Thr Leu Glu Ala Val Ala Ala Leu Gly Asn Lys Val
 130 135 140
 Val Glu Ser Leu Arg Ala Gln Asp Pro Ser Glu Val Leu Thr Met Leu
 145 150 155 160
 Thr Asn Glu Thr Gly Phe Glu Ile Ser Ser Ser Asp Ala Thr Val Lys
 165 170 175
 Ile Leu Ile Thr Thr Val Pro Pro Asn Leu Arg Lys Leu Asp Pro Glu
 180 185 190
 Leu His Leu Asp Ile Lys Val Leu Gln Ser Ala Leu Ala Ala Ile Arg
 195 200 205
 His Ala Arg Trp Phe Glu Glu Asn Ala Ser Gln Ser Thr Val Lys Val
 210 215 220
 Leu Ile Arg Leu Leu Lys Asp Leu Arg Ile Arg Phe Pro Gly Phe Glu
 225 230 235 240
 Pro Leu Thr Pro Trp Ile Leu Asp Leu Leu Gly His Tyr Ala Val Met
 245 250 255
 Asn Asn Pro Thr Arg Gln Pro Leu Ala Leu Asn Val Ala Tyr Arg Arg
 260 265 270
 Cys Leu Gln Ile Leu Ala Ala Gly Leu Phe Leu Pro Gly Ser Val Gly
 275 280 285
 Ile Thr Asp Pro Cys Glu Ser Gly Asn Phe Arg Val His Thr Val Met
 290 295 300

467

Thr Leu Glu Gln Gln Asp Met Val Cys Tyr Thr Ala Gln Thr Leu Val
 305 310 315 320
 Arg Ile Leu Ser His Gly Gly Phe Arg Lys Ile Leu Gly Gln Glu Gly
 325 330 335
 Asp Ala Ser Tyr Leu Ala Ser Glu Ile Ser Thr Trp Asp Gly Val Ile
 340 345 350
 Val Thr Pro Ser Glu Lys Ala Tyr Glu Lys Pro Pro Glu Lys Lys Glu
 355 360 365
 Gly Glu Glu Glu Glu Glu Asn Thr Glu Glu Pro Pro Gln Gly Glu Glu
 370 375 380
 Glu Glu Ser Met Glu Thr Gln Glu
 385 390

<210> 511
 <211> 72
 <212> PRT
 <213> Homo sapiens

<400> 511
 His Gly Gly Gly Lys Gly Arg Gln Val Gly Leu His Ser Val Gln Arg
 1 5 10 15
 Pro Ala Arg Arg Glu Thr Ala Ala Ser Trp Gly Leu Cys Val Lys Ile
 20 25 30
 Pro Asp Leu Gly Val Ala Phe Val Tyr Lys Met Gln Glu Gly Lys Pro
 35 40 45
 Val Pro Asp Ser Ser Arg Gln His Ala Gln Leu Ser Gly Ser Pro Val
 50 55 60
 Ser Gln Gly Leu Ser Leu Pro Leu
 65 70

<210> 512
 <211> 181
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (33)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 512

Gly	Trp	Cys	Ser	Cys	Ala	His	Ser	Ser	Ala	Trp	Pro	Gly	Xaa	Trp	Gly
1				5					10					15	

Ala	Ser	Gly	Ile	Pro	Gln	Gln	Ala	Pro	Met	Thr	Val	Cys	Asp	Gln	Ala
			20					25					30		

Xaa	Pro	Val	Thr	Phe	Leu	Leu	Leu	His	Leu	Glu	Gly	Gly	Asp	Ile	His
		35					40					45			

Thr	Val	Ser	His	Leu	Ser	Ser	Pro	Pro	Pro	Gly	Val	Ala	His	Arg	Met
	50					55					60				

Gly	Thr	Gly	Gly	Ser	Arg	Asn	Pro	Asn	Pro	Ala	Trp	Leu	Gly	Gly	Ala
65					70					75					80

Leu	Leu	Val	Arg	Gly	Arg	Pro	Ala	Ser	Leu	Ala	Pro	Trp	Gly	His	Ser
				85					90					95	

Trp	Lys	Arg	Gly	Leu	Ala	His	Ala	Pro	Leu	Arg	Ala	Gly	Thr	Cys	Thr
			100					105					110		

Gly	His	Thr	Arg	His	Ser	Ala	Cys	Trp	Asn	Arg	Trp	Leu	Cys	Ser	Cys
		115					120					125			

Ser	Gly	Pro	Arg	Ala	Ala	Xaa	Leu	Arg	Pro	Cys	Thr	Ser	His	Met	His
	130					135					140				

Trp	Thr	Arg	Ala	Glu	Thr	Pro	Val	Cys	Tyr	Arg	Ala	Leu	Val	Leu	Cys
145					150					155					160

Gly	Pro	Gly	Ala	Thr	Ala	Gln	Ser	Ser	Gln	Trp	Arg	Ser	Thr	Pro	Leu
				165					170					175	

Asp	Ser	Ile	Phe	Phe
			180	

469

<210> 513

<211> 202

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (15)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 513

Leu Gly Asp Thr Ile Glu Gly Thr Pro Ala Gly Thr Val Pro Xaa Phe
 1 5 10 15

Pro Gly Arg Pro Thr Arg Ala Ile Met Ala Gln Asp Gln Gly Glu Lys
 20 25 30

Glu Asn Pro Met Arg Glu Leu Arg Ile Arg Lys Leu Cys Leu Asn Ile
 35 40 45

Cys Val Gly Glu Ser Gly Asp Arg Leu Thr Arg Ala Ala Lys Val Leu
 50 55 60

Glu Gln Leu Thr Gly Gln Thr Pro Val Phe Ser Lys Ala Arg Tyr Thr
 65 70 75 80

Val Arg Ser Phe Gly Ile Arg Arg Asn Glu Lys Ile Ala Val His Cys
 85 90 95

Thr Val Arg Gly Ala Lys Ala Glu Glu Ile Leu Glu Lys Gly Leu Lys
 100 105 110

Val Arg Glu Tyr Glu Leu Arg Lys Asn Asn Phe Ser Asp Thr Gly Asn
 115 120 125

Phe Gly Phe Gly Ile Gln Glu His Ile Asp Leu Gly Ile Lys Tyr Asp
 130 135 140

Pro Ser Ile Gly Ile Tyr Gly Leu Asp Phe Tyr Val Val Leu Gly Arg
 145 150 155 160

Pro Gly Phe Ser Ile Ala Asp Lys Lys Arg Arg Thr Gly Cys Ile Gly
 165 170 175

Ala Lys His Arg Ile Ser Lys Glu Glu Ala Met Arg Trp Phe Gln Gln
 180 185 190

Lys Tyr Asp Gly Ile Ile Leu Pro Gly Lys
 195 200

470

<210> 514
 <211> 63
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (2)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (5)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (16)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (35)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 514
 Xaa Xaa Lys Asn Xaa Ile Thr Pro Lys Glu Glu Ser Pro Pro His Xaa
 1 5 10 15
 Ala Leu Leu Ser Lys Cys Leu Leu Thr Pro Ser Pro Lys Met Pro Pro
 20 25 30
 Ile Leu Xaa Val Met Ala Ala Leu Gly Phe Glu Arg Arg Glu Phe Gly
 35 40 45
 Ser Thr Ser Val Glu Arg Val Gln Ser Arg Gln Leu Asp Cys Phe
 50 55 60

<210> 515
 <211> 218
 <212> PRT
 <213> Homo sapiens

471

<220>

<221> SITE

<222> (151)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (209)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (211)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 515

Ser Leu Ala Arg Gly Cys Gln Arg Pro Asp Ala Val Leu Tyr Ala Arg
 1 5 10 15

His Tyr Asn Ile Pro Val Ile His Ala Phe Arg Arg Ala Val Asp Asp
 20 25 30

Pro Gly Leu Val Phe Asn Gln Leu Pro Lys Met Leu Tyr Pro Glu Tyr
 35 40 45

His Lys Val His Gln Met Met Arg Glu Gln Ser Ile Leu Ser Pro Ser
 50 55 60

Pro Tyr Glu Gly Tyr Arg Ser Leu Pro Arg His Gln Leu Leu Cys Phe
 65 70 75 80

Lys Glu Asp Cys Gln Ala Val Phe Gln Asp Leu Glu Gly Val Glu Lys
 85 90 95

Val Phe Gly Val Ser Leu Val Leu Val Leu Ile Gly Ser His Pro Asp
 100 105 110

Leu Ser Phe Leu Pro Gly Ala Gly Ala Asp Phe Ala Val Asp Pro Asp
 115 120 125

Gln Pro Leu Ser Ala Lys Arg Asn Pro Ile Asp Val Asp Pro Phe Thr
 130 135 140

Tyr Gln Ser Thr Arg Gln Xaa Gly Leu Tyr Ala Met Gly Pro Leu Ala
 145 150 155 160

Gly Asp Asn Phe Val Arg Phe Val Gln Gly Gly Ala Leu Ala Val Ala
 165 170 175

Ser Ser Leu Leu Arg Lys Glu Gln Asn His Leu His Arg Gln Pro Trp
 180 185 190

472

Ser Ser Leu Arg Gly Ile His Pro Leu Ile Asp Leu Lys Ser Gly Val
195 200 205

Xaa Pro Xaa Leu Val Lys Leu Thr Ala Gln
210 215

<210> 516

<211> 41

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 516

Asn Gly Arg Pro Asp Ser Thr Gly Pro Ala Ile Pro Gly Ile Leu Ser
1 5 10 15

Trp Gly Phe Glu Thr Xaa Leu Arg Asp Arg Glu Thr Asp Pro Arg Asn
20 25 30

Val Leu Asn Cys Asn Gly Pro His Thr
35 40

<210> 517

<211> 250

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (118)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (161)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (204)

<223> Xaa equals any of the naturally occurring L-amino acids

473

<400> 517

Gly Phe Asn Arg Ser Phe Cys Gly Arg Asn Ala Thr Val Tyr Gly Lys
 1 5 10 15

Gly Val Tyr Phe Ala Arg Arg Ala Ser Leu Ser Val Gln Asp Arg Tyr
 20 25 30

Ser Pro Pro Asn Ala Asp Gly His Lys Ala Val Phe Val Ala Arg Val
 35 40 45

Leu Thr Gly Asp Tyr Gly Gln Gly Arg Arg Gly Leu Arg Ala Pro Pro
 50 55 60

Leu Arg Gly Pro Gly His Val Leu Leu Arg Tyr Asp Ser Ala Val Asp
 65 70 75 80

Cys Ile Cys Gln Pro Ser Ile Phe Val Ile Phe His Asp Thr Gln Ala
 85 90 95

Leu Pro Thr His Leu Ile Thr Cys Glu Ala Arg Ala Pro Arg Phe Pro
 100 105 110

Arg Arg Pro Leu Trp Xaa Pro Gly Pro Leu Pro Arg His Leu Thr Glu
 115 120 125

Gly Ala Thr Leu Trp Pro Pro Ala Ser Gln Ala Pro Ser Ser Ala Gln
 130 135 140

Ala Asp Ala Pro Arg Pro Gln Leu Trp Pro Pro Glu Leu Ser Pro Gly
 145 150 155 160

Xaa Pro Cys Leu Pro Leu Arg Ala Pro Glu Gly Gly Val Gly Asp Gly
 165 170 175

Gly Gln Gln Arg Pro Arg Gly Ala Gly Leu Gly Pro Ser Leu Gly Arg
 180 185 190

Pro His His Gln Gly Ser Ala Glu Pro Arg Arg Xaa His Arg Pro Pro
 195 200 205

Ala Ala Pro Arg Pro Arg Pro Ser Arg Leu Cys Cys Leu Asn Lys Arg
 210 215 220

Glu Arg Glu Pro Arg Arg Lys Gly Pro Gly Lys Lys Lys Lys Lys Lys
 225 230 235 240

Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
 245 250

474

<210> 518
 <211> 100
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (3)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 518
 Asn Pro Xaa Lys Lys Leu Xaa Ile Leu Ile Lys Trp Pro Pro Pro Phe
 1 5 10 15
 Pro Pro Ser Phe Pro Pro Ser Pro Asn Ser Leu Ser Ser Ser Ser Phe
 20 25 30
 Pro Pro Pro Leu Ser Leu Phe Ser Pro Ser Phe Thr Phe Leu Ile Ser
 35 40 45
 Val Lys Leu Glu Arg Phe Glu Ile Pro Ile Lys Val Arg Leu Ser Pro
 50 55 60
 Glu Pro Trp Thr Pro Glu Thr Gly Leu Val Thr Asp Ala Phe Lys Leu
 65 70 75 80
 Lys Arg Lys Glu Leu Arg Asn His Tyr Leu Lys Asp Ile Glu Arg Met
 85 90 95
 Tyr Gly Gly Lys
 100

<210> 519
 <211> 60
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (5)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE

475

<222> (17)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 519

His Glu Asp Gly Xaa Leu Met Gly Cys Arg His Arg Trp His Pro Arg
 1 5 10 15

Xaa Val Pro Phe His Gln Thr Ser Pro Lys Thr Glu Leu Glu Ser Thr
 20 25 30

Ile Phe Gly Ser Pro Arg Leu Ala Ser Gly Leu Phe Pro Glu Trp Gln
 35 40 45

Ser Trp Gly Arg Met Glu Asn Leu Ala Ser Tyr Arg
 50 55 60

<210> 520

<211> 120

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 520

Ser His Pro Tyr Ala Pro Ser Cys Gly Leu Arg Gly Pro Gly Ala Ala
 1 5 10 15

Ser Arg Ala Arg Thr Arg Glu Arg Xaa Pro Gln Ala Glu Ala Glu Ala
 20 25 30

Arg Ser Thr Pro Gly Pro Ala Gly Ser Arg Leu Gly Pro Glu Thr Phe
 35 40 45

Arg Gln Arg Phe Arg Gln Phe Arg Tyr Gln Asp Ala Ala Gly Pro Arg
 50 55 60

Glu Ala Phe Arg Gln Leu Arg Glu Leu Ser Arg Gln Trp Leu Arg Pro
 65 70 75 80

Asp Ile Arg Thr Lys Glu Gln Ile Val Glu Met Leu Val Gln Glu Gln
 85 90 95

Leu Leu Ala Ile Leu Pro Glu Ala Ala Arg Ala Arg Arg Ile Arg Arg
 100 105 110

Arg Thr Asp Val Arg Ile Thr Gly

476

115

120

<210> 521

<211> 96

<212> PRT

<213> Homo sapiens

<400> 521

Gly His Gln Thr Val Ser Pro Ser Thr Gly Ser Arg Val Thr Arg Met
 1 5 10 15

Phe Ser Leu Ile Ser Phe Ser His Val Phe Ile Lys Asp Ile Cys Lys
 20 25 30

Leu Pro Lys Asp Glu Gly Thr Cys Arg Asp Phe Ile Leu Lys Trp Tyr
 35 40 45

Tyr Asp Pro Asn Thr Lys Ser Cys Ala Arg Phe Trp Tyr Gly Gly Cys
 50 55 60

Gly Gly Asn Glu Asn Lys Phe Gly Ser Gln Lys Glu Cys Glu Lys Val
 65 70 75 80

Cys Ala Pro Val Leu Ala Lys Pro Gly Val Ile Ser Val Met Gly Thr
 85 90 95

<210> 522

<211> 122

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (18)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 522

Asn Ser Gly Phe Arg Pro Lys Asn Pro Val Gly Arg Gly Gly Glu Pro
 1 5 10 15

Glu Xaa Cys Gly Gly Ala Gly Gly Leu Gly Cys Thr Leu Val Trp Gly
 20 25 30

Gly Thr Gly Ala Ala Val Val Thr Gly Val Val Trp Leu Leu Leu Pro

477

35 40 45
 Asn Gly Gly Val Gly Val Gly Leu Leu Gly Pro Gln Ser Pro Val Gly
 50 55 60
 Gly Ser Asp Ser Ala Pro Tyr Ser Leu His Pro Ala Gly Arg Thr Trp
 65 70 75 80
 Gly Leu Arg Ser Glu Cys Ile Pro Pro Leu Ser Phe Asn Leu Ser Cys
 85 90 95
 Arg Thr His Ser Gly Pro Gly Ala Arg Leu Gly Glu Ala Gly Pro Asn
 100 105 110
 Tyr Gly Ser Arg Glu Leu Gln Val Pro Thr
 115 120

<210> 523

<211> 94

<212> PRT

<213> Homo sapiens

<400> 523

Leu Ile Pro Gln Val Cys Cys Lys His Ser Met Glu Asp Thr Asp Asp
 1 5 10 15
 Ser Leu Val Leu Val Phe Leu Ser Ala Val Asn Val Gln Gln Phe Ala
 20 25 30
 Gln Glu Leu Gly Asp His Ile Cys Leu Ser Gly Gln Gly Ser Glu Val
 35 40 45
 His Trp Asn Leu Leu Arg Asn Leu Phe Val Lys Thr Ile Val Asn Asn
 50 55 60
 Tyr Cys Ile Phe Leu Gln Lys Tyr Ile Leu Glu Asn Cys Ile Leu Ser
 65 70 75 80
 Ile Lys Val Phe Leu Cys Lys Lys Lys Lys Lys Lys Leu Val
 85 90

<210> 524

<211> 93

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (86)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (93)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 524

Ser	Ala	Val	Met	Gly	Arg	Lys	Lys	Lys	Lys	Gln	Leu	Lys	Pro	Trp	Cys
1				5					10					15	

Trp	Tyr	Cys	Asn	Arg	Asp	Phe	Asp	Asp	Glu	Lys	Ile	Leu	Ile	Gln	His
			20					25					30		

Gln	Lys	Ala	Lys	His	Phe	Lys	Cys	His	Ile	Cys	His	Lys	Lys	Leu	Tyr
	35						40					45			

Thr	Gly	Pro	Gly	Leu	Ala	Ile	His	Cys	Met	Gln	Val	His	Lys	Glu	Thr
	50					55					60				

Ile	Asp	Ala	Val	Pro	Asn	Ala	Tyr	Leu	Gly	Glu	Gln	Thr	Xaa	Ile	Gly
65					70					75					80

Asn	Ile	Trp	Tyr	Gly	Xaa	Tyr	Ser	Arg	Lys	Arg	Tyr	Xaa
				85					90			

<210> 525

<211> 324

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (323)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 525

Asp	Leu	Arg	Leu	Ser	Arg	Pro	Glu	Ala	Val	Glu	Ala	Glu	Ala	Met	Met
1				5					10					15	

Ala	Ala	Met	Ala	Thr	Ala	Arg	Val	Arg	Met	Gly	Pro	Arg	Cys	Ala	Gln
			20					25					30		

Ala Leu Trp Arg Met Pro Trp Leu Pro Val Phe Leu Ser Leu Ala Ala
 35 40 45
 Ala Ala Ala Ala Ala Ala Ala Glu Gln Gln Val Pro Leu Val Leu Trp
 50 55 60
 Ser Ser Asp Arg Asp Leu Trp Ala Pro Ala Ala Asp Thr His Glu Gly
 65 70 75 80
 His Ile Thr Ser Asp Leu Gln Leu Ser Thr Tyr Leu Asp Pro Ala Leu
 85 90 95
 Glu Leu Gly Pro Arg Asn Val Leu Leu Phe Leu Gln Asp Lys Leu Ser
 100 105 110
 Ile Glu Asp Phe Thr Ala Tyr Gly Gly Val Phe Gly Asn Lys Gln Asp
 115 120 125
 Ser Ala Phe Ser Asn Leu Glu Asn Ala Leu Asp Leu Ala Pro Ser Ser
 130 135 140
 Leu Val Leu Pro Ala Val Asp Trp Tyr Ala Val Ser Thr Leu Thr Thr
 145 150 155 160
 Tyr Leu Gln Glu Lys Leu Gly Ala Ser Pro Leu His Val Asp Leu Ala
 165 170 175
 Thr Leu Arg Glu Leu Lys Leu Asn Ala Ser Leu Pro Ala Leu Leu Leu
 180 185 190
 Ile Arg Leu Pro Tyr Thr Ala Ser Ser Gly Leu Met Ala Pro Arg Glu
 195 200 205
 Val Leu Thr Gly Asn Asp Glu Val Ile Gly Gln Val Leu Ser Thr Leu
 210 215 220
 Lys Ser Glu Asp Val Pro Tyr Thr Ala Ala Leu Thr Ala Val Arg Pro
 225 230 235 240
 Ser Arg Val Ala Arg Asp Val Ala Val Val Ala Gly Gly Leu Gly Arg
 245 250 255
 Gln Leu Leu Gln Lys Gln Pro Val Ser Pro Val Ile His Pro Pro Val
 260 265 270
 Ser Tyr Asn Asp Thr Ala Pro Arg Ile Leu Phe Trp Ala Gln Asn Phe
 275 280 285
 Ser Val Ala Tyr Lys Asp Gln Trp Glu Asp Leu Thr Pro Leu Thr Phe
 290 295 300

480

Gly Val Gln Glu Leu Asn Leu Thr Gly Ser Phe Trp Asn Asp Ser Phe
 305 310 315 320

Ala Ser Xaa His

<210> 526

<211> 66

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 526

Phe Xaa Val Ser Trp Thr Trp Lys Gln Val Ser Glu Phe Pro Gly Asp
 1 5 10 15

Gln Arg Asp Glu Val Leu Gln Leu Pro Pro Ser Ser Cys Asn Leu Val
 20 25 30

Ser Ser Gly Ala Gly Gly Glu Pro Glu Lys Leu Ala Ser Tyr Ile Thr
 35 40 45

Ser Leu Trp Leu Phe Phe Ile Cys Lys Thr Arg Ile Ile Leu Asn Cys
 50 55 60

Lys Gly
 65

<210> 527

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (40)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 527

Asn Thr Gln Leu Trp Phe Leu Cys Phe Pro Asn Cys Lys Ala Ala Asp
 1 5 10 15

481

Asn Lys Thr Pro Gly Phe His Val Ser Ser Ala Met Ser Thr Leu Thr
 20 25 30
 Gln Ile Leu Lys Gln Asn Ser Xaa Asn Ala Val Leu Arg Ile Gln Leu
 35 40 45
 Leu Leu Lys Pro Ile Ser Ile Cys Ile Ile Thr Thr Asn Ile
 50 55 60

<210> 528

<211> 122

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (104)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (105)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 528

Tyr Asn Lys Ile Glu Ile Met His Leu Val Met Trp Pro Thr Ser Leu
 1 5 10 15
 Leu Thr Thr Met Asp Cys Phe Gln Gln Gln Leu Ile Phe Trp Ser Val
 20 25 30
 Leu Arg Gly Ala Cys Met Ser Phe Val Thr Ser Gly Ser Thr Pro Ala
 35 40 45
 Val Lys Tyr Cys Phe His Leu Pro Leu Gln Lys Ala Ser Cys Leu Leu
 50 55 60
 Thr Ser Thr Ala Lys Ala Leu Phe Trp Thr Gly Tyr Leu Ile Lys Xaa
 65 70 75 80
 Ile Ser Val Arg Leu Cys Ser Val Ile Pro Ser Glu Pro Arg Phe Val
 85 90 95
 Ser Lys Ala Thr Val Leu Ser Xaa Xaa Pro Cys Val Trp Gly Gln Val

482

100	105	110
Ala Ile Pro Pro Met Ser Leu Val Ile Leu		
115	120	

<210> 529
 <211> 182
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (25)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 529
 Asp Arg Thr Arg Leu Ser Gln Ala Ser Thr Pro Thr Pro Val Cys Trp
 1 5 10 15
 Gly Leu Leu Gln Pro Pro Pro Trp Xaa Glu Ala Trp Tyr Arg Leu Thr
 20 25 30
 His Arg Gly Leu Cys Gln Val Arg Phe Cys Arg Trp Ser Gln Ala Leu
 35 40 45
 Pro Glu Ala Arg Gly Gly Ala Trp Ala Gly Ser Pro Gly Glu Gly Gln
 50 55 60
 Ala Gly Pro Arg Leu His Thr His Ile Gln Pro Ala Gly Leu Ser Ala
 65 70 75 80
 Val Leu Ser Pro Ser Leu Ser Ser Pro Ser Ser Ala Val Thr Leu Ser
 85 90 95
 Ser Pro Ser Leu Pro Ala Ser Pro Pro Ala Ala Pro Pro Val Lys Arg
 100 105 110
 Met Thr Lys Asp Leu Ser Tyr Ala Gly Ser Lys Asn Gln Asn Phe Leu
 115 120 125
 Leu Ala Phe Ser Phe Val Ala Ser Pro Ala Pro Ala Leu Pro Val Ser
 130 135 140
 His Pro Gly Pro Arg Leu Glu Ala Ser Leu His Leu Ser Tyr Cys Phe
 145 150 155 160
 Lys Pro Lys Phe Thr Val Ser Val Gly Gly Gln Asp Leu Leu Ser Pro
 165 170 175

483

Pro Leu Leu His Pro Pro
180

<210> 530

<211> 183

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (6)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (79)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (81)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 530

Ala Leu Val Leu Gly Xaa Lys Ser Val Arg Met Ala Ser Ser Arg Met
1 5 10 15

Thr Arg Arg Asp Pro Leu Thr Asn Lys Val Ala Leu Val Thr Ala Ser
20 25 30

Thr Asp Gly Ile Gly Phe Ala Ser Pro Gly Val Trp Pro Arg Thr Gly
35 40 45

Pro Arg Gly Arg Gln Gln Pro Glu Ala Ala Glu Cys Gly Pro Gly Gly
50 55 60

Gly Thr Leu Gln Gly Glu Gly Leu Ser Val Thr Gly Thr Cys Xaa Xaa
65 70 75 80

Xaa Gly Lys Ala Glu Asp Arg Glu Arg Leu Val Ala Thr Ala Val Lys
85 90 95

Leu His Gly Gly Ile Asp Ile Leu Val Ser Asn Ala Ala Val Asn Pro
100 105 110

484

Phe	Phe	Gly	Ser	Ile	Met	Asp	Val	Thr	Glu	Glu	Val	Trp	Asp	Lys	Leu	
						120			125							
<hr/>																
Trp	Met	Asp	Lys	Glu	Lys	Glu	Glu	Ser	Met	Lys	Glu	Thr	Leu	Arg	Ile	
						135			140							
<hr/>																
Arg	Arg	Leu	Gly	Glu	Pro	Glu	Asp	Cys	Ala	Gly	Ile	Val	Ser	Phe	Leu	
					150			155							160	
<hr/>																
Cys	Ser	Glu	Asp	Ala	Ser	Tyr	Ile	Thr	Gly	Glu	Thr	Val	Val	Val	Gly	
				165			170							175		
<hr/>																
Gly	Gly	Thr	Pro	Ser	Arg	Leu										
							180									

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<210> 531
<211> 129
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (89)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (103)
<223> xaa equals any of the naturally occurring L-amino acids
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```

<400> 531
Asn Ser Ala Pro Leu Ser Pro Thr Gly Leu Gly Gln Gly His Thr Gly
 1             5             10             15
His Val Arg Phe Leu Ala Ala Val Gln Leu Pro Asp Gly Phe Asn Leu
      20             25             30
Leu Cys Pro Thr Pro Pro Pro Pro Pro Asp Thr Gly Pro Glu Lys Leu
      35             40             45
Pro Ser Leu Glu His Arg Asp Ser Pro Trp His Arg Gly Pro Ala Pro
      50             55             60
Ala Arg Pro Lys Met Leu Val Ile Ser Gly Gly Asp Gly Tyr Glu Asp
      65             70             75             80
Phe Arg Leu Ser Ser Gly Gly Gly Xaa Ala Val Arg Leu Trp Val Glu
      85             90             95

```

485

Thr Thr Ala Gln Thr Thr Xaa Ser Cys Gly Gly Cys Asp Pro Val Cys
 100 105 110

Arg Gly Pro Gly Leu Ala Arg Pro Pro Ala Phe Ser Leu Leu Ala Ser
 115 120 125

Pro

<210> 532

<211> 91

<212> PRT

<213> Homo sapiens

<400> 532

Gly Ala Ile Ala Ser Ser Gly Pro Thr Gly Gly Arg Val Arg Lys His
 1 5 10 15

Gln Leu Leu Pro Gly Ala Val Arg Glu Trp Glu Gln Leu Trp Ala Pro
 20 25 30

His Phe Arg Gln Val Leu Pro Lys Pro Ser Asp Ala Val Arg Pro Gly
 35 40 45

Leu Pro Val Val Leu Phe Arg Leu Cys Phe Gln Asn Ala Phe Ile Ser
 50 55 60

Ser Val Pro Phe Gly Pro His Lys Ser Pro Trp Gly Val Gly Gly Gly
 65 70 75 80

Leu Cys Arg His Pro His Phe Lys Ala Gly Ser
 85 90

<210> 533

<211> 67

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (63)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 533

Asn Leu Cys Gln Val Gln Pro Thr Arg Leu Tyr Ser Ser Leu His Ser
 1 5 10 15

486

Gly Leu His His Val Arg Gln Val Thr Gln Lys Ser Tyr Lys Val Ser
 20 25 30
 Thr Ser Gly Pro Arg Ala Phe Ser Ser Arg Ser Tyr Thr Ser Gly Pro
 35 40 45
 Gly Ser Arg Ile Ser Ser Ser Ala Phe Ser Arg Val Gly Gly Xaa Ser
 50 55 60
 Gly Gly Ala
 65

<210> 534
 <211> 144
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (140)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (141)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 534
 Phe Asn Arg Arg Tyr Pro Lys Ile Gln Phe Ser Leu Ser Thr Gly Pro
 1 5 10 15
 Ser Gly Thr Met Leu Asp Gly Val Leu Glu Gly Lys Leu Asn Ala Ala
 20 25 30
 Phe Ile Asp Gly Pro Ile Asn His Thr Ala Ile Asp Gly Ile Pro Val
 35 40 45
 Tyr Arg Glu Glu Leu Met Ile Val Thr Pro Gln Gly Tyr Ala Pro Val
 50 55 60
 Thr Arg Ala Ser Gln Val Asn Gly Ser Asn Ile Tyr Ala Phe Arg Ala
 65 70 75 80
 Asn Cys Ser Tyr Arg Arg His Phe Glu Ser Trp Phe His Ala Asp Gly
 85 90 95
 Ala Ala Pro Gly Thr Ile His Glu Met Glu Ser Tyr His Gly Met Leu
 100 105 110

487

Ala Cys Val Ile Ala Gly Ala Gly Ile Ala Leu Ile Pro Arg Ser Met
 115 120 125

Leu Glu Ser Met Pro Gly His His Gln Val Glu Xaa Xaa Ala Val Ser
 130 135 140

<210> 535

<211> 175

<212> PRT

<213> Homo sapiens

<400> 535

Arg Ala Pro Ala Arg Ile Ser Gly Gly Gly Ser Ala Met Val Gly Gly
 1 5 10 15

Gly Gly Val Gly Gly Gly Leu Leu Glu Asn Ala Asn Pro Leu Ile Tyr
 20 25 30

Gln Arg Ser Gly Glu Arg Pro Val Thr Ala Gly Glu Glu Asp Glu Gln
 35 40 45

Val Pro Asp Ser Ile Asp Ala Arg Glu Ile Phe Asp Leu Ile Arg Ser
 50 55 60

Ile Asn Asp Pro Glu His Pro Leu Thr Leu Glu Glu Leu Asn Val Val
 65 70 75 80

Glu Gln Val Arg Val Gln Val Ser Asp Pro Glu Ser Thr Val Ala Val
 85 90 95

Ala Phe Thr Pro Thr Ile Pro His Cys Ser Met Ala Thr Leu Ile Gly
 100 105 110

Leu Ser Ile Lys Val Lys Leu Leu Arg Ser Leu Pro Gln Arg Phe Lys
 115 120 125

Met Asp Val His Ile Thr Pro Gly Thr His Ala Ser Glu His Ala Val
 130 135 140

Asn Lys Gln Leu Ala Asp Lys Glu Arg Val Ala Ala Ala Leu Glu Asn
 145 150 155 160

Thr His Leu Leu Glu Val Val Asn Gln Cys Leu Ser Ala Arg Ser
 165 170 175

488

<210> 536

<211> 148

<212> PRT

<213> Homo sapiens

<400> 536

Gly Trp His Arg Thr His His Arg Gly Arg His Gln Ala Arg Glu Ala
 1 5 10 15

Glu Glu Glu Ala Trp Ala Ala Ala Glu Pro Ile Lys Lys Val Arg Lys
 20 25 30

Ser Leu Ala Leu Asp Ile Val Asp Glu Asp Val Lys Leu Met Met Ser
 35 40 45

Thr Leu Pro Lys Ser Leu Ser Leu Pro Thr Thr Ala Pro Ser Asn Ser
 50 55 60

Ser Ser Leu Thr Leu Ser Gly Ile Lys Glu Asp Asn Ser Leu Leu Asn
 65 70 75 80

Gln Gly Phe Leu Gln Ala Lys Pro Glu Lys Ala Ala Val Ala Gln Lys
 85 90 95

Pro Arg Ser His Phe Thr Thr Pro Ala Pro Met Ser Ser Ala Trp Lys
 100 105 110

Thr Val Ala Cys Gly Gly Thr Arg Asp Gln Leu Phe Met Gln Glu Lys
 115 120 125

Ala Arg Gln Leu Leu Gly Arg Leu Lys Pro Ser His Thr Ser Arg Thr
 130 135 140

Leu Ile Leu Ser
 145

<210> 537

<211> 70

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

489

<221> SITE

<222> (42)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 537

Arg	Pro	Thr	Arg	Ser	Ala	Trp	Trp	Gly	Arg	Leu	Leu	Ser	Arg	Val	Ser
1				5				10					15		

Pro	Gln	Pro	Arg	Pro	Ala	Ser	Pro	Ser	Val	Ser	Thr	Arg	Asn	Gln	Leu
			20					25					30		

Pro	Glu	Ala	Arg	Arg	Gly	Val	Glu	Xaa	Xaa	Glu	Cys	Glu	Glu	Thr	Ala
		35					40					45			

Ala	Ser	Ala	Glu	Arg	Ala	Gly	Pro	Pro	Arg	Ala	Leu	Val	Phe	Gly	Ala
	50					55					60				

Gln	Ser	Arg	Ser	Pro	Gly
65					70

<210> 538

<211> 206

<212> PRT

<213> Homo sapiens

<400> 538

Gly	Glu	Val	Ser	Ala	Ser	Gly	Ile	Ala	Arg	Arg	Gly	Gly	Pro	Met	Ala
1				5				10					15		

Pro	Leu	Gly	Gly	Ala	Pro	Arg	Leu	Val	Leu	Leu	Phe	Ser	Gly	Lys	Arg
		20					25						30		

Lys	Ser	Gly	Lys	Asp	Phe	Val	Thr	Glu	Ala	Leu	Gln	Ser	Arg	Leu	Gly
		35					40					45			

Ala	Asp	Val	Cys	Ala	Val	Leu	Arg	Leu	Ser	Gly	Pro	Leu	Lys	Glu	Gln
	50					55						60			

Tyr	Ala	Gln	Glu	His	Gly	Leu	Asn	Phe	Gln	Arg	Leu	Leu	Asp	Thr	Ser
65					70					75					80

Thr	Tyr	Lys	Glu	Ala	Phe	Arg	Lys	Asp	Met	Ile	Arg	Trp	Gly	Glu	Glu
				85						90				95	

Lys	Arg	Gln	Ala	Asp	Pro	Gly	Phe	Phe	Cys	Arg	Lys	Ile	Val	Glu	Gly
		100					105						110		

Ile	Ser	Gln	Pro	Ile	Trp	Leu	Val	Ser	Asp	Thr	Arg	Arg	Val	Ser	Asp
				115			120						125		

490

Ile Gln Trp Phe Arg Glu Ala Tyr Gly Ala Val Thr Gln Thr Val Arg
 130 135 140

Val Val Ala Leu Glu Gln Ser Arg Gln Gln Arg Gly Trp Val Phe Thr
 145 150 155 160

Pro Gly Val Asp Asp Ala Glu Ser Glu Cys Gly Leu Asp Asn Phe Gly
 165 170 175

Asp Phe Asp Trp Val Ile Glu Asn His Gly Val Glu Gln Arg Leu Glu
 180 185 190

Glu Gln Leu Glu Asn Leu Ile Glu Phe Ile Arg Ser Arg Leu
 195 200 205

<210> 539

<211> 350

<212> PRT

<213> Homo sapiens

<400> 539

Ser Thr Leu Ile Ala Phe Ile Val Ile Ser Thr Leu Phe Pro Leu Leu
 1 5 10 15

Asp Met Thr Glu Ile Tyr Phe Ser Leu Leu Asp Glu Ile Val Asp Thr
 20 25 30

Leu Gly Glu Gly Ala Phe Gly Lys Val Val Glu Cys Ile Asp His Lys
 35 40 45

Ala Gly Gly Arg His Val Ala Val Lys Ile Val Lys Asn Val Asp Arg
 50 55 60

Tyr Cys Glu Ala Ala Arg Ser Glu Ile Gln Val Leu Glu His Leu Asn
 65 70 75 80

Thr Thr Asp Pro Asn Ser Thr Phe Arg Cys Val Gln Met Leu Glu Trp
 85 90 95

Phe Glu His His Gly His Ile Cys Ile Val Phe Glu Leu Leu Gly Leu
 100 105 110

Ser Thr Tyr Asp Phe Ile Lys Glu Asn Gly Phe Leu Pro Phe Arg Leu
 115 120 125

Asp His Ile Arg Lys Met Ala Tyr Gln Ile Cys Lys Ser Val Asn Phe
 130 135 140

491

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Leu His Ser Asn Lys Leu Thr His Thr Asp Leu Lys Pro Glu Asn Ile
145                      150                      155                      160

Leu Phe Val Gln Ser Asp Tyr Thr Glu Ala Tyr Asn Pro Lys Ile Lys
                      165                      170                      175

Arg Asp Glu Arg Thr Leu Ile Asn Pro Asp Ile Lys Val Val Asp Phe
                      180                      185                      190

Gly Ser Ala Thr Tyr Asp Asp Glu His His Ser Thr Leu Val Ser Thr
                      195                      200                      205

Arg His Tyr Arg Ala Pro Glu Val Ile Leu Ala Leu Gly Trp Ser Gln
210                      215                      220

Pro Cys Asp Val Trp Ser Ile Gly Cys Ile Leu Ile Glu Tyr Tyr Leu
225                      230                      235                      240

Gly Phe Thr Val Phe Pro Thr His Asp Ser Lys Glu His Leu Ala Met
                      245                      250                      255

Met Glu Arg Ile Leu Gly Pro Leu Pro Lys His Met Ile Gln Lys Thr
                      260                      265                      270

Arg Lys Arg Lys Tyr Phe His His Asp Arg Leu Asp Trp Asp Glu His
275                      280                      285

Ser Ser Ala Gly Arg Tyr Val Ser Arg Arg Cys Lys Pro Leu Lys Glu
290                      295                      300

Phe Met Leu Ser Gln Asp Val Glu His Glu Arg Leu Phe Asp Leu Ile
305                      310                      315                      320

Gln Lys Met Leu Glu Tyr Asp Pro Ala Lys Arg Ile Thr Leu Arg Glu
                      325                      330                      335

Ala Leu Lys His Pro Phe Phe Asp Leu Leu Lys Lys Ser Ile
340                      345                      350

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<210> 540

<211> 324

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (54)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (56)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (297)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (304)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (305)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (317)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (321)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 540

Gln	Ala	Thr	Met	Gly	Asn	Val	Leu	Ala	Ala	Ser	Ser	Pro	Pro	Ala	Gly
1				5					10					15	

Pro	Pro	Pro	Pro	Pro	Ala	Pro	Ala	Leu	Val	Gly	Leu	Pro	Pro	Pro	Pro
				20				25						30	

Pro	Ser	Pro	Pro	Gly	Phe	Thr	Leu	Pro	Pro	Leu	Gly	Gly	Ser	Leu	Gly
				35			40						45		

Ala	Gly	Thr	Ser	Thr	Xaa	Arg	Xaa	Ser	Glu	Arg	Thr	Pro	Gly	Ala	Ala
				50			55					60			

Thr	Ala	Ser	Ala	Ser	Gly	Ala	Ala	Glu	Asp	Gly	Ala	Cys	Gly	Cys	Leu
				65			70				75				80

Pro	Asn	Pro	Gly	Thr	Phe	Glu	Glu	Cys	His	Arg	Lys	Cys	Lys	Glu	Leu
				85					90					95	

Phe	Pro	Ile	Gln	Met	Glu	Gly	Val	Lys	Leu	Thr	Val	Asn	Lys	Gly	Leu
				100					105					110	

493

Ser Asn His Phe Gln Val Asn His Thr Val Ala Leu Ser Thr Ile Gly
 115 120 125

Glu Ser Asn Tyr His Phe Gly Val Thr Tyr Val Gly Thr Lys Gln Leu
 130 135 140

Ser Pro Thr Glu Ala Phe Pro Val Leu Val Gly Asp Met Asp Asn Ser
 145 150 155 160

Gly Ser Leu Asn Ala Gln Val Ile His Gln Leu Gly Pro Gly Leu Arg
 165 170 175

Ser Lys Met Ala Ile Gln Thr Gln Gln Ser Lys Phe Val Asn Trp Gln
 180 185 190

Val Asp Gly Glu Tyr Arg Gly Ser Asp Phe Thr Ala Ala Val Thr Leu
 195 200 205

Gly Asn Pro Asp Val Leu Val Gly Ser Gly Ile Leu Val Ala His Tyr
 210 215 220

Leu Gln Ser Ile Thr Pro Cys Leu Ala Leu Gly Gly Glu Leu Val Tyr
 225 230 235 240

His Arg Arg Pro Gly Glu Glu Gly Thr Val Met Ser Leu Ala Gly Lys
 245 250 255

Tyr Thr Leu Asn Asn Trp Leu Ala Thr Val Thr Leu Gly Gln Ala Gly
 260 265 270

Met His Ala Thr Tyr Tyr His Lys Ala Ser Asp Gln Leu Gln Val Gly
 275 280 285

Val Glu Phe Glu Ala Ser Thr Arg Xaa Gln Asp Thr Ser Val Ser Xaa
 290 295 300

Xaa Val Pro Ala Trp Asn Leu Pro Lys Gly Gln Pro Xaa Leu Ser Lys
 305 310 315 320

Xaa Leu Leu Gly

<210> 541

<211> 204

<212> PRT

<213> Homo sapiens

<400> 541

494

```

Arg Gly Pro Thr Phe Thr Pro Glu Ile Met Ala Ala Glu Asp Val Val
 1           5           10           15

Ala Thr Gly Ala Asp Pro Ser Asp Leu Glu Ser Gly Gly Leu Leu His
      20           25           30

Glu Ile Phe Thr Ser Pro Leu Asn Leu Leu Leu Gly Leu Cys Ile
      35           40           45

Phe Leu Leu Tyr Lys Ile Val Arg Gly Asp Gln Pro Ala Ala Ser Gly
      50           55           60

Asp Ser Asp Asp Asp Glu Pro Pro Pro Leu Pro Arg Leu Lys Arg Arg
      65           70           75           80

Asp Phe Thr Pro Ala Glu Leu Arg Arg Phe Asp Gly Val Gln Asp Pro
      85           90           95

Arg Ile Leu Met Ala Ile Asn Gly Lys Val Phe Asp Val Thr Lys Gly
      100          105          110

Arg Lys Phe Tyr Gly Pro Glu Gly Pro Tyr Gly Val Phe Ala Gly Arg
      115          120          125

Asp Ala Ser Arg Gly Leu Ala Thr Phe Cys Leu Asp Lys Glu Ala Leu
      130          135          140

Lys Asp Glu Tyr Asp Asp Leu Ser Asp Leu Thr Ala Ala Gln Gln Glu
      145          150          155          160

Thr Leu Ser Asp Trp Glu Ser Gln Phe Thr Phe Lys Tyr His His Val
      165          170          175

Gly Lys Leu Leu Lys Glu Gly Glu Glu Pro Thr Val Tyr Ser Asp Glu
      180          185          190

Glu Glu Pro Lys Asp Glu Ser Ala Arg Lys Asn Asp
      195          200

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<210> 542

<211> 193

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (183)

<223> Xaa equals any of the naturally occurring L-amino acids

495

<400> 542

Pro Ala Tyr Ser Leu Gly Leu Leu Lys Ser Val Leu Asp Gly Gly Gly
 1 5 10 15
 Ala Gly Ala His Gln Ala Arg Ser Asn Pro Ser Cys Met Tyr Pro Gln
 20 25 30
 Gly Thr Phe Val Ile Pro Leu Leu Val Thr Ala His Arg Asp Pro Thr
 35 40 45
 Gln Phe Lys Asp Pro Asp Cys Phe Asn Pro Thr Asn Phe Leu Asp Lys
 50 55 60
 Gly Lys Phe Gln Gly Asn Asp Ala Phe Met Pro Phe Ala Ser Gly Ala
 65 70 75 80
 Gly Arg Gly Gly Arg Gly Pro Ala Trp Thr Gly Ser Gly Val Pro Gly
 85 90 95
 Ala His Cys Ala Pro Val Tyr Pro Ala Lys Gln Met Cys Leu Gly Thr
 100 105 110
 Gly Leu Ala His Ser Gly Ile Phe Leu Phe Leu Thr Ala Thr Leu Gln
 115 120 125
 Arg Phe Cys Leu Leu Pro Val Val Arg Pro Gly Thr Ile Asn Leu Thr
 130 135 140
 Cys Ser Ala Leu Ala Trp Ala Val Ser Pro Gln Thr Ser Ser Ser Ser
 145 150 155 160
 Gln Trp Pro Ala Glu Val Arg Leu His Tyr Gly Gly Leu Thr Gly Pro
 165 170 175
 Gln Thr Ser Ile Pro Ser Xaa Val Asn Lys Gly Pro Lys Leu Gln Lys
 180 185 190

Lys

<210> 543

<211> 352

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (154)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (167)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 543

Ser Thr Val Arg Xaa Pro Gly Arg Pro Thr Arg Pro Met Ala Ala Glu
 1 5 10 15

Glu Pro Gln Gln Gln Lys Gln Glu Pro Leu Gly Ser Asp Ser Glu Val
 20 25 30

Leu Thr Val Trp Pro Met Met Lys Pro Ser Trp Leu Ser Arg Thr Glu
 35 40 45

Phe Ser Lys Arg Leu Leu Cys Arg Thr Leu Trp Cys Gln Ser Gly Trp
 50 55 60

Ser Ser Arg Ser Tyr Thr Arg Ser Met Leu Lys Met Thr Thr Ser Ile
 65 70 75 80

Asn Arg Arg Ser Arg Thr Ser Thr Lys Ser Thr Arg Thr Ser Ala Arg
 85 90 95

Pro Gly Leu Thr Ala Thr Val Ser Ile Gly Leu Ser Asp Ser Pro Thr
 100 105 110

Trp Arg His Cys Trp Met Thr Ala Arg Ser Cys Ser Gly Glu Lys Gly
 115 120 125

Gly His Trp Ala Pro Arg Gln Val Gly Val Tyr Leu Leu Pro Gly Arg
 130 135 140

Val Gly Cys Val Ser Ser Arg Val Ser Xaa Ser Phe Pro Gly Asp Gly
 145 150 155 160

Leu Asp Ser Gly Leu Ala Xaa Arg Gly Ser Ala Val Ser Ala Leu Ala
 165 170 175

Ser Gly Leu Val Glu Glu Pro Met Leu Gly Pro Pro Phe His Pro Thr
 180 185 190

Pro Arg Phe Lys Ala Val Ser Ala Lys Ser Lys Glu Asp Leu Val Ser
 195 200 205

497

Gln Gly Phe Thr Glu Phe Thr Ile Glu Asp Phe His Asn Thr Phe Met
 210 215 220
 Asp Leu Ile Glu Gln Val Glu Lys Gln Thr Ser Val Ala Asp Leu Leu
 225 230 235 240
 Ala Ser Phe Asn Asp Gln Ser Thr Ser Asp Tyr Leu Val Val Tyr Leu
 245 250 255
 Arg Leu Leu Thr Ser Gly Tyr Leu Gln Arg Glu Ser Lys Phe Phe Glu
 260 265 270
 His Phe Ile Glu Gly Gly Arg Thr Val Lys Glu Phe Cys Gln Gln Glu
 275 280 285
 Val Glu Pro Met Cys Lys Glu Ser Asp His Ile His Ile Ile Ala Leu
 290 295 300
 Ala Gln Ala Leu Ser Val Ser Ile Gln Val Glu Tyr Met Asp Arg Gly
 305 310 315 320
 Glu Gly Gly Thr Thr Asn Pro His Ile Phe Pro Glu Gly Ser Glu Pro
 325 330 335
 Lys Val Tyr Leu Leu Tyr Arg Pro Gly His Tyr Asp Ile Leu Tyr Lys
 340 345 350

<210> 544

<211> 240

<212> PRT

<213> Homo sapiens

<400> 544

Ser Thr His Ala Ser Glu Met Ala Glu Arg Gly Tyr Ser Phe Ser Leu
 1 5 10 15
 Thr Thr Phe Ser Pro Ser Gly Lys Leu Val Gln Ile Glu Tyr Ala Leu
 20 25 30
 Ala Ala Val Ala Gly Gly Ala Pro Ser Val Gly Ile Lys Ala Ala Asn
 35 40 45
 Gly Val Val Leu Ala Thr Glu Lys Lys Gln Lys Ser Ile Leu Tyr Asp
 50 55 60
 Glu Arg Ser Val His Lys Val Glu Pro Ile Thr Lys His Ile Gly Leu

498

```

65              70              75              80
Val Tyr Ser Gly Met Gly Pro Asp Tyr Arg Val Leu Val His Arg Ala
              85              90              95
Arg Lys Leu Ala Gln Gln Tyr Tyr Leu Val Tyr Gln Glu Pro Ile Pro
              100             105             110
Thr Ala Gln Leu Val Gln Arg Val Ala Ser Val Met Gln Glu Tyr Thr
              115             120             125
Gln Ser Gly Gly Val Arg Pro Phe Gly Val Ser Leu Leu Ile Cys Gly
              130             135             140
Trp Asn Glu Gly Arg Pro Tyr Leu Phe Gln Ser Asp Pro Ser Gly Ala
              145             150             155             160
Tyr Phe Ala Trp Lys Ala Thr Ala Met Gly Lys Asn Tyr Val Asn Gly
              165             170             175
Lys Thr Phe Leu Glu Lys Arg Tyr Asn Glu Asp Leu Glu Leu Glu Asp
              180             185             190
Ala Ile His Thr Ala Ile Leu Thr Leu Lys Glu Ser Phe Glu Gly Gln
              195             200             205
Met Thr Glu Asp Asn Ile Glu Val Gly Ile Cys Asn Glu Ala Gly Phe
              210             215             220
Arg Arg Leu Thr Pro Thr Glu Val Lys Asp Tyr Leu Ala Ala Ile Ala
              225             230             235             240

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<210> 545

<211> 181

<212> PRT

<213> Homo sapiens

<400> 545

```

Arg Cys Ile Leu Tyr Thr Gly Phe Met Leu Gly Ala Gln Arg Glu Val
  1              5              10             15
Asp Ser Arg Leu Leu Ala Leu Pro Gly Arg Lys Val Pro Thr Ser Trp
              20              25              30
Trp Asp Asp Leu Phe Lys Gly Ala Lys Glu His Gly Ala Val Ala Val
              35              40              45

```

499

Glu Arg Val Thr Lys Ser Pro Gly Glu Thr Ser Lys Pro Arg Pro Phe
 50 55 60
 Ala Gly Gly Gly Tyr Arg Leu Gly Ala Ala Pro Glu Glu Glu Ser Ala
 65 70 75 80
 Tyr Val Ala Gly Glu Lys Arg Gln His Ser Ser Gln Asp Val His Val
 85 90 95
 Val Leu Lys Leu Trp Lys Ser Gly Phe Ser Leu Asp Asn Gly Glu Leu
 100 105 110
 Arg Ser Tyr Gln Asp Pro Ser Asn Ala Gln Phe Leu Glu Ser Ile Arg
 115 120 125
 Arg Gly Glu Val Pro Ala Glu Leu Arg Arg Leu Ala His Gly Gly Gln
 130 135 140
 Val Asn Leu Asp Met Glu Asp His Arg Asp Glu Asp Phe Val Lys Pro
 145 150 155 160
 Lys Gly Ala Phe Lys Ala Phe Thr Gly Glu Gly Gln Lys Leu Gly Ser
 165 170 175
 Thr Ala Pro Arg Cys
 180

<210> 546

<211> 197

<212> PRT

<213> Homo sapiens

<400> 546

Pro Arg Val Arg Arg Arg Ala Arg Ala Ala Ala Gly Ser Ser His Ala
 1 5 10 15
 Ala Met Ala Asp Ser Glu Leu Gln Leu Val Glu Gln Arg Ile Arg Ser
 20 25 30
 Phe Pro Asp Phe Pro Thr Pro Gly Val Val Phe Arg Asp Ile Ser Pro
 35 40 45
 Val Leu Lys Asp Pro Ala Ser Phe Arg Ala Ala Ile Gly Leu Leu Ala
 50 55 60
 Arg His Leu Lys Ala Thr His Gly Gly Arg Ile Asp Tyr Ile Ala Gly
 65 70 75 80

500

Leu Asp Ser Arg Gly Phe Leu Phe Gly Pro Ser Leu Ala Gln Glu Leu
 85 90 95
 Gly Leu Gly Cys Val Leu Ile Arg Lys Arg Gly Lys Leu Pro Gly Pro
 100 105 110
 Thr Leu Trp Ala Ser Tyr Ser Leu Glu Tyr Gly Lys Ala Glu Leu Glu
 115 120 125
 Ile Gln Lys Asp Ala Leu Glu Pro Gly Gln Arg Val Val Val Val Asp
 130 135 140
 Asp Leu Leu Ala Thr Gly Gly Thr Met Asn Ala Ala Cys Glu Leu Leu
 145 150 155 160
 Gly Arg Leu Gln Ala Glu Val Leu Glu Cys Val Ser Leu Val Glu Leu
 165 170 175
 Thr Ser Leu Lys Gly Arg Glu Lys Leu Ala Pro Val Pro Phe Phe Ser
 180 185 190
 Leu Leu Gln Tyr Glu
 195

<210> 547

<211> 93

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (84)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 547

Glu Thr Gly Lys Glu Ser Lys Ala Leu Phe Leu Pro Phe Pro Gly Ser
 1 5 10 15
 Val Tyr Ser Thr Ser Thr Gly Glu Ala Ser Gly Glu Gly Leu Ser Pro
 20 25 30
 Leu Pro His Leu His Glu Phe Trp Asn Ser Val Leu Leu Ala Ala Cys
 35 40 45
 Phe Gln Leu Pro Pro Ile Ser Ile Ala Ala Gly Ser Ser Cys Leu Phe
 50 55 60
 Tyr Ser Val Ile Lys His Pro Ala Pro Thr Leu Ser Gln Arg Ser Ile
 65 70 75 80

501

Leu Ile Leu Xaa Lys Lys Ile Tyr Glu Glu Lys Lys Lys
 85 90

<210> 548

<211> 49

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 548

Gly Leu Gln Leu Xaa Ala His Ala Ala Gly Arg Val Pro Gly Cys Ala
 1 5 10 15

Leu Gln Gly Leu Gly His Phe Leu Gln Glu Asn Lys Gln Leu Leu Arg
 20 25 30

Asp Val Leu Ala Gln Glu Leu His Lys Pro Ala Phe Glu Gly Arg His
 35 40 45

Ile

<210> 549

<211> 379

<212> PRT

<213> Homo sapiens

<400> 549

Val Ala Cys Cys Val Arg Ile Pro Gly Pro Pro Arg Arg Ser Gly Pro
 1 5 10 15

Ala Met Ala Val Thr Ile Thr Leu Lys Thr Leu Gln Gln Gln Thr Phe
 20 25 30

Lys Ile Arg Met Glu Pro Asp Glu Thr Val Lys Val Leu Lys Glu Lys
 35 40 45

Ile Glu Ala Glu Lys Gly Arg Asp Ala Phe Pro Val Ala Gly Gln Lys
 50 55 60

Leu Ile Tyr Ala Gly Lys Ile Leu Ser Asp Asp Val Pro Ile Arg Asp
 65 70 75 80

Tyr Arg Ile Asp Glu Lys Asn Phe Val Val Val Met Val Thr Lys Thr
 85 90 95
 Lys Ala Gly Gln Gly Thr Ser Ala Pro Pro Glu Ala Ser Pro Thr Ala
 100 105 110
 Ala Pro Glu Ser Ser Thr Ser Phe Pro Pro Ala Pro Thr Ser Gly Met
 115 120 125
 Ser His Pro Pro Pro Ala Ala Arg Glu Asp Lys Ser Pro Ser Glu Glu
 130 135 140
 Ser Ala Pro Thr Thr Ser Pro Glu Ser Val Ser Gly Ser Val Pro Ser
 145 150 155 160
 Ser Gly Ser Ser Gly Arg Glu Glu Asp Ala Ala Ser Thr Leu Val Thr
 165 170 175
 Gly Ser Glu Tyr Glu Thr Met Leu Thr Glu Ile Met Ser Met Gly Tyr
 180 185 190
 Glu Arg Glu Arg Val Val Ala Ala Leu Arg Ala Ser Tyr Asn Asn Pro
 195 200 205
 His Arg Ala Val Glu Tyr Leu Leu Thr Gly Ile Pro Gly Ser Pro Glu
 210 215 220
 Pro Glu His Gly Ser Val Gln Glu Ser Gln Val Ser Glu Gln Pro Ala
 225 230 235 240
 Thr Glu Ala Gly Glu Asn Pro Leu Glu Phe Leu Arg Asp Gln Pro Gln
 245 250 255
 Phe Gln Asn Met Arg Gln Val Ile Gln Gln Asn Pro Ala Leu Leu Pro
 260 265 270
 Ala Leu Leu Gln Gln Leu Gly Gln Glu Asn Pro Gln Leu Leu Gln Gln
 275 280 285
 Ile Ser Arg His Gln Glu Gln Phe Ile Gln Met Leu Asn Glu Pro Pro
 290 295 300
 Gly Glu Leu Ala Asp Ile Ser Asp Val Glu Gly Glu Val Gly Ala Ile
 305 310 315 320
 Gly Glu Glu Ala Pro Gln Met Asn Tyr Ile Gln Val Thr Pro Gln Glu
 325 330 335
 Lys Glu Ala Ile Glu Arg Leu Lys Ala Leu Gly Phe Pro Glu Ser Leu
 340 345 350

503

Val Ile Gln Ala Tyr Phe Ala Cys Glu Lys Asn Glu Asn Leu Ala Ala
355 360 365

Asn Phe Leu Leu Ser Gln Asn Phe Asp Asp Glu
370 375

<210> 550

<211> 275

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (6)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (235)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (260)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (261)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (267)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (272)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 550

Cys Ser Cys Lys Arg Xaa His Gln Gln Gln Val Leu Pro Pro Arg Gln
1 5 10 15

Pro Ser Ala Leu Val Pro Ser Val Thr Glu Tyr Arg Leu Asp Gly His
20 25 30

504

Thr Ile Ser Asp Leu Ser Arg Ser Ser Arg Gly Glu Leu Ile Pro Ile
 35 40 45
 Ser Pro Ser Thr Glu Val Gly Gly Ser Gly Ile Gly Thr Pro Pro Ser
 50 55 60
 Val Leu Lys Arg Gln Arg Lys Arg Arg Val Ala Leu Ser Pro Val Thr
 65 70 75 80
 Glu Asn Ser Thr Ser Leu Ser Phe Leu Asp Ser Cys Asn Ser Leu Thr
 85 90 95
 Pro Lys Ser Thr Pro Val Lys Thr Leu Pro Phe Ser Pro Ser Gln Phe
 100 105 110
 Leu Asn Phe Trp Asn Lys Gln Asp Thr Leu Glu Leu Glu Ser Pro Ser
 115 120 125
 Leu Thr Ser Thr Pro Val Cys Ser Gln Lys Val Val Val Thr Thr Pro
 130 135 140
 Leu His Arg Asp Lys Thr Pro Leu His Gln Lys His Ala Ala Phe Val
 145 150 155 160
 Thr Pro Asp Gln Lys Tyr Ser Met Asp Asn Thr Pro His Thr Pro Thr
 165 170 175
 Pro Phe Lys Asn Ala Leu Glu Lys Tyr Gly Pro Leu Lys Pro Leu Pro
 180 185 190
 Gln Thr Pro His Leu Glu Glu Asp Leu Lys Glu Val Leu Arg Ser Glu
 195 200 205
 Ala Gly Ile Glu Leu Ile Ile Glu Asp Asp Ile Arg Pro Glu Lys Gln
 210 215 220
 Lys Arg Lys Pro Gly Leu Arg Arg Ser Pro Xaa Lys Lys Val Arg Lys
 225 230 235 240
 Ser Leu Ala Leu Asp Ile Val Asp Glu Asp Val Lys Leu Met Met Ser
 245 250 255
 Thr Leu Pro Xaa Xaa Leu Ser Leu Ala Thr Xaa Ala Pro Cys Lys Xaa
 260 265 270
 Phe Gln Pro
 275

<210> 551

505

<211> 161

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (158)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 551

Asn Leu Ala Ala Ala Ser Gly Gly Gly Pro Gln Ser Val Ser Gly Thr
 1 5 10 15

Leu Leu Cys Glu Pro Val Leu Thr Met Phe Ala Thr Ser Gly Ala Val
 20 25 30

Ala Ala Gly Lys Pro Tyr Ser Cys Ser Glu Cys Gly Lys Ser Phe Cys
 35 40 45

Tyr Ser Ser Val Leu Leu Arg His Glu Arg Ala His Gly Gly Asp Gly
 50 55 60

Arg Phe Arg Cys Leu Glu Cys Gly Glu Arg Cys Ala Arg Ala Ala Asp
 65 70 75 80

Leu Arg Ala His Arg Arg Thr His Ala Gly Gln Thr Leu Tyr Ile Cys
 85 90 95

Ser Glu Cys Gly Gln Ser Phe Arg His Ser Gly Arg Leu Asp Leu His
 100 105 110

Leu Gly Ala His Arg Gln Arg Cys Arg Thr Cys Pro Cys Arg Thr Cys
 115 120 125

Gly Arg Arg Phe Pro His Leu Pro Ala Leu Leu Leu His Arg Arg Arg
 130 135 140

Gln His Leu Pro Glu Arg Pro Arg Arg Cys Pro Leu Cys Xaa Leu Arg
 145 150 155 160

Phe

<210> 552

<211> 405

<212> PRT

<213> Homo sapiens

<400> 552

506

Pro Arg Val Arg Arg Arg Ala Arg Gly Arg Arg Val Arg Pro Ala Gly
 1 5 10 15
 Gly Pro Val Arg Arg Gly Ala Ala Val Arg Gly Ala Leu Arg Gly Ala
 20 25 30
 Ser Leu Gly His Gly Ala Ala Ala Arg Ala Gly Arg Pro Leu Cys Val
 35 40 45
 Arg His Ser Glu Pro Val Cys Gly Ser Asp Ala Asn Thr Tyr Ala Asn
 50 55 60
 Leu Cys Gln Leu Arg Ala Ala Ser Arg Arg Ser Glu Arg Leu His Arg
 65 70 75 80
 Pro Pro Val Ile Val Leu Gln Arg Gly Ala Cys Gly Gln Gly Gln Glu
 85 90 95
 Asp Pro Asn Ser Leu Arg His Lys Tyr Asn Phe Ile Ala Asp Val Val
 100 105 110
 Glu Lys Ile Ala Pro Ala Val Val His Ile Glu Leu Phe Arg Lys Leu
 115 120 125
 Pro Phe Ser Lys Arg Glu Val Pro Val Ala Ser Gly Ser Gly Phe Ile
 130 135 140
 Val Ser Glu Asp Gly Leu Ile Val Thr Asn Ala His Val Val Thr Asn
 145 150 155 160
 Lys His Arg Val Lys Val Glu Leu Lys Asn Gly Ala Thr Tyr Glu Ala
 165 170 175
 Lys Ile Lys Asp Val Asp Glu Lys Ala Asp Ile Ala Leu Ile Lys Ile
 180 185 190
 Asp His Gln Gly Lys Leu Pro Val Leu Leu Leu Gly Arg Ser Ser Glu
 195 200 205
 Leu Arg Pro Gly Glu Phe Val Val Ala Ile Gly Ser Pro Phe Ser Leu
 210 215 220
 Gln Asn Thr Val Thr Thr Gly Ile Val Ser Thr Thr Gln Arg Gly Gly
 225 230 235 240
 Lys Glu Leu Gly Leu Arg Asn Ser Asp Met Asp Tyr Ile Gln Thr Asp
 245 250 255
 Ala Ile Ile Asn Tyr Gly Asn Ser Gly Gly Pro Leu Val Asn Leu Asp
 260 265 270

507

Gly Glu Val Ile Gly Ile Asn Thr Leu Lys Val Thr Ala Gly Ile Ser
 275 280 285
 Phe Ala Ile Pro Ser Asp Lys Ile Lys Lys Phe Leu Thr Glu Ser His
 290 295 300
 Asp Arg Gln Ala Lys Gly Lys Ala Ile Thr Lys Lys Lys Tyr Ile Gly
 305 310 315 320
 Ile Arg Met Met Ser Leu Thr Ser Ser Lys Ala Lys Glu Leu Lys Asp
 325 330 335
 Arg His Arg Asp Phe Pro Asp Val Ile Ser Gly Ala Tyr Ile Ile Glu
 340 345 350
 Val Ile Pro Asp Thr Pro Ala Glu Ala Gly Gly Leu Lys Glu Asn Asp
 355 360 365
 Val Ile Ile Ser Ile Asn Gly Gln Ser Val Val Ser Ala Asn Asp Val
 370 375 380
 Ser Asp Val Ile Lys Arg Glu Ser Thr Leu Asn Met Val Val Arg Arg
 385 390 395 400
 Val Met Lys Ile Ser
 405

<210> 553

<211> 107

<212> PRT

<213> Homo sapiens

<400> 553

Ala Gln Glu Asn Glu Glu Met Glu Gln Pro Met Gln Asn Gly Glu Glu
 1 5 10 15
 Asp Arg Pro Leu Gly Gly Gly Glu Gly His Gln Pro Ala Gly Asn Arg
 20 25 30
 Arg Gly Gln Ala Arg Arg Leu Ala Pro Asn Phe Arg Trp Ala Ile Pro
 35 40 45
 Asn Arg Gln Ile Asn Asp Gly Met Gly Gly Asp Gly Asp Asp Met Glu
 50 55 60
 Ile Phe Met Glu Glu Met Arg Glu Ile Arg Arg Lys Leu Arg Glu Leu
 65 70 75 80
 Gln Leu Arg Asn Cys Leu Arg Ile Leu Met Gly Glu Leu Ser Asn His

508

	85	90	95
His Asp His His Asp Glu Phe Cys Leu Met Pro			
100	105		

<210> 554
 <211> 229
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (8)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (15)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (20)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (27)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (78)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 554
 Gly Leu Ser Ala Glu Ser Thr Xaa Thr Ser Thr Met Pro Met Xaa Leu
 1 5 10 15
 Gly Tyr Trp Xaa Ile Arg Gly Leu Ala His Xaa Ile Arg Leu Leu Leu
 20 25 30
 Glu Tyr Thr Asp Ser Ser Tyr Glu Glu Lys Lys Tyr Thr Met Gly Asp
 35 40 45
 Ala Pro Asp Tyr Asp Arg Ser Gln Trp Leu Asn Glu Lys Phe Lys Leu
 50 55 60
 Gly Leu Asp Phe Pro Asn Leu Pro Tyr Leu Ile Asp Gly Xaa His Lys

509

[illegible]

<210> 555

<211> 106

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (59)

<223> xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (60)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

510

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (98)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 555

Asn Val Ile Ser Val Asp Pro Asn Asp Gln Lys Lys Thr Ala Cys Tyr
 1 5 10 15

Asp Ile Asp Val Glu Val Asp Asp Thr Leu Lys Thr Gln Met Asn Ser
 20 25 30

Phe Leu Leu Ser Thr Ala Ser Gln Gln Glu Ile Ala Thr Leu Asp Asn
 35 40 45

Lys Thr Met Thr Asp Val Val Gly Asn Gln Xaa Xaa Ser Ala Glu Leu
 50 55 60

Ser Ser Thr Ser Ser Pro Gly Xaa Gly Gly Cys Val Pro Ile Leu Leu
 65 70 75 80

Leu Gln Gly Ala Ala Glu Thr Thr Arg Ile Arg Ala Ser Pro Gly Asn
 85 90 95

Pro Xaa Tyr Ile Gly Pro Leu Pro Gln Pro
 100 105

<210> 556

<211> 86

<212> PRT

<213> Homo sapiens

<400> 556

Gly Arg Ala Thr Lys Gln Asn Thr Thr Lys Pro Asn His Arg Ile Ile
 1 5 10 15

Phe Asn Pro Thr Phe Tyr Thr Met Pro Gln Phe Pro Ile Thr Leu His
 20 25 30

Thr Ser Phe Cys Val Gln Leu Asn Cys Asn Cys Phe Leu Tyr Leu Glu
 35 40 45

Arg Val Thr Ile Glu Leu Glu Thr Phe Tyr Ser Gly Arg Leu Gly Ser
 50 55 60

Phe Trp Trp Asp Ser Val Gly Glu Arg Glu Glu Gly Glu Val Gly Gly

511

65	70	75	80
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Leu Leu Pro Phe Arg Thr
 85

<210> 557
 <211> 565
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (57)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (71)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (75)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (82)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (118)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (120)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (552)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 557
 Ala Ser Leu Thr Gly Thr Gln Ala Leu Pro Pro Leu Phe Ser Leu Gly
 1 5 10 15

512

Tyr His Gln Ser Arg Trp Asn Tyr Arg Asp Glu Ala Asp Val Leu Glu
 20 25 30
 Val Asp Gln Gly Phe Asp Asp His Asn Leu Pro Cys Asp Val Ile Trp
 35 40 45
 Leu Asp Ile Glu His Ala Asp Gly Xaa Arg Tyr Phe Thr Trp Asp Pro
 50 55 60
 Ser Arg Phe Pro Gln Pro Xaa Thr Met Leu Xaa Arg Leu Ala Ser Lys
 65 70 75 80
 Arg Xaa Lys Leu Val Ala Ile Val Asp Pro His Ile Lys Val Asp Ser
 85 90 95
 Gly Tyr Arg Val His Glu Glu Leu Arg Asn Leu Gly Leu Tyr Val Lys
 100 105 110
 Thr Arg Asp Gly Ser Xaa Tyr Xaa Gly Trp Cys Trp Pro Gly Ser Ala
 115 120 125
 Gly Tyr Pro Asp Phe Thr Asn Pro Thr Met Arg Ala Trp Trp Ala Asn
 130 135 140
 Met Phe Ser Tyr Asp Asn Tyr Glu Gly Ser Ala Pro Asn Leu Phe Val
 145 150 155 160
 Trp Asn Asp Met Asn Glu Pro Ser Val Phe Asn Gly Pro Glu Val Thr
 165 170 175
 Met Leu Lys Asp Ala Gln His Tyr Gly Gly Trp Glu His Arg Asp Val
 180 185 190
 His Asn Ile Tyr Gly Leu Tyr Val His Met Ala Thr Ala Asp Gly Leu
 195 200 205
 Arg Gln Arg Ser Gly Gly Met Glu Arg Pro Phe Val Leu Ala Arg Ala
 210 215 220
 Phe Phe Ala Gly Ser Gln Arg Phe Gly Ala Val Trp Thr Gly Asp Asn
 225 230 235 240
 Thr Ala Glu Trp Asp His Leu Lys Ile Ser Ile Pro Met Cys Leu Ser
 245 250 255
 Leu Gly Leu Val Gly Leu Ser Phe Cys Gly Ala Asp Val Gly Gly Phe
 260 265 270
 Phe Lys Asn Pro Glu Pro Glu Leu Leu Val Arg Trp Tyr Gln Met Gly
 275 280 285

513

Ala Tyr Gln Pro Phe Phe Arg Ala His Ala His Leu Asp Thr Gly Arg
 290 295 300
 Arg Glu Pro Trp Leu Leu Pro Ser Gln His Asn Asp Ile Ile Arg Asp
 305 310 315 320
 Ala Leu Gly Gln Arg Tyr Ser Leu Leu Pro Phe Trp Tyr Thr Leu Leu
 325 330 335
 Tyr Gln Ala His Arg Glu Gly Ile Pro Val Met Arg Pro Leu Trp Val
 340 345 350
 Gln Tyr Pro Gln Asp Val Thr Thr Phe Asn Ile Asp Asp Gln Tyr Leu
 355 360 365
 Leu Gly Asp Ala Leu Leu Val His Pro Val Ser Asp Ser Gly Ala His
 370 375 380
 Gly Val Gln Val Tyr Leu Pro Gly Gln Gly Glu Val Trp Tyr Asp Ile
 385 390 395 400
 Gln Ser Tyr Gln Lys His His Gly Pro Gln Thr Leu Tyr Leu Pro Val
 405 410 415
 Thr Leu Ser Ser Ile Pro Val Phe Gln Arg Gly Gly Thr Ile Val Pro
 420 425 430
 Arg Trp Met Arg Val Arg Arg Ser Ser Glu Cys Met Lys Asp Asp Pro
 435 440 445
 Ile Thr Leu Phe Val Ala Leu Ser Pro Gln Gly Thr Ala Gln Gly Glu
 450 455 460
 Leu Phe Leu Asp Asp Gly His Thr Phe Asn Tyr Gln Thr Arg Gln Glu
 465 470 475 480
 Phe Leu Leu Arg Arg Phe Ser Phe Ser Gly Asn Thr Leu Val Ser Ser
 485 490 495
 Ser Ala Asp Pro Glu Gly His Phe Glu Thr Pro Ile Trp Ile Glu Arg
 500 505 510
 Val Val Ile Ile Gly Ala Gly Lys Pro Ala Ala Val Val Leu Gln Thr
 515 520 525
 Lys Gly Ser Pro Glu Ser Arg Leu Ser Phe Gln His Asp Pro Glu Thr
 530 535 540
 Ser Val Leu Val Leu Arg Lys Xaa Gly Ile Asn Val Ala Ser Asp Trp
 545 550 555 560

514

Ser Ile His Leu Arg
565

<210> 558

<211> 160

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (39)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 558

Arg Glu Ala Val Leu Pro Gln Ala Val Leu Arg His Pro Val Arg Thr
1 5 10 15

Gln Arg Arg Glu His Arg Gly Arg Gly Leu Leu His Leu Arg Glu Ala
20 25 30

Pro Gly Gly Gly Ala Ala Xaa His Arg Pro His Arg Gly Pro Arg Gly
35 40 45

Pro Ser Arg Gly Ala Glu Gly Glu Arg Pro Pro Glu Gly Pro Ser Arg
50 55 60

Ala Ser Ser Val Thr Thr Phe Thr Gly Glu Pro Asn Thr Cys Pro Arg
65 70 75 80

Cys Ser Lys Lys Val Tyr Phe Ala Glu Lys Val Thr Ser Leu Gly Lys
85 90 95

Asp Trp His Arg Pro Cys Leu Arg Cys Glu Arg Cys Gly Lys Thr Leu
100 105 110

Thr Pro Gly Gly His Ala Glu His Asp Gly Gln Pro Tyr Cys His Lys
115 120 125

Pro Cys Tyr Gly Ile Leu Phe Gly Pro Lys Gly Val Asn Thr Gly Ala
130 135 140

Val Gly Ser Tyr Ile Tyr Asp Arg Asp Pro Glu Gly Lys Val Gln Pro
145 150 155 160

515

<210> 559

<211> 480

<212> PRT

<213> Homo sapiens

<400> 559

Gly Cys Ile Gly Tyr Leu Val Leu Leu Trp Pro Leu Pro Leu Ile His
 1 5 10 15

Phe Gly Leu Ala Asn Gln Ser Glu Asp Leu Ser Val Phe Tyr Pro Gly
 20 25 30

Thr Leu Leu Glu Thr Gly His Asp Ile Leu Phe Phe Trp Val Ala Arg
 35 40 45

Met Val Met Leu Gly Leu Lys Leu Thr Gly Arg Leu Pro Phe Arg Glu
 50 55 60

Val Tyr Leu His Ala Ile Val Arg Asp Ala His Gly Arg Lys Met Ser
 65 70 75 80

Lys Ser Leu Gly Asn Val Ile Asp Pro Leu Asp Val Ile Tyr Gly Ile
 85 90 95

Ser Leu Gln Gly Leu His Asn Gln Leu Leu Asn Ser Asn Leu Asp Pro
 100 105 110

Ser Glu Val Glu Lys Ala Lys Glu Gly Gln Lys Ala Asp Phe Pro Ala
 115 120 125

Gly Ile Pro Glu Cys Gly Thr Asp Ala Leu Arg Phe Gly Leu Cys Ala
 130 135 140

Tyr Met Ser Gln Gly Arg Asp Ile Asn Leu Asp Val Asn Arg Ile Leu
 145 150 155 160

Gly Tyr Arg His Phe Cys Asn Lys Leu Trp Asn Ala Thr Lys Phe Ala
 165 170 175

Leu Arg Gly Leu Gly Lys Gly Phe Val Pro Ser Pro Thr Ser Gln Pro
 180 185 190

Gly Gly His Glu Ser Leu Val Asp Arg Trp Ile Arg Ser Arg Leu Thr
 195 200 205

Glu Ala Val Arg Leu Ser Asn Gln Gly Phe Gln Ala Tyr Asp Phe Pro
 210 215 220

Ala Val Thr Thr Ala Gln Tyr Ser Phe Trp Leu Tyr Glu Leu Cys Asp
 225 230 235 240

516

Val Tyr Leu Glu Cys Leu Lys Pro Val Leu Asn Gly Val Asp Gln Val
 245 250 255
 Ala Ala Glu Cys Ala Arg Gln Thr Leu Tyr Thr Cys Leu Asp Val Gly
 260 265 270
 Leu Arg Leu Leu Ser Pro Phe Met Pro Phe Val Thr Glu Glu Leu Phe
 275 280 285
 Gln Arg Leu Pro Arg Arg Met Pro Gln Ala Pro Pro Ser Leu Cys Val
 290 295 300
 Thr Pro Tyr Pro Glu Pro Ser Glu Cys Ser Trp Lys Asp Pro Glu Ala
 305 310 315 320
 Glu Ala Ala Leu Glu Leu Ala Leu Ser Ile Thr Arg Ala Val Arg Ser
 325 330 335
 Leu Arg Ala Asp Tyr Asn Leu Thr Arg Ile Arg Pro Asp Cys Phe Leu
 340 345 350
 Glu Val Ala Asp Glu Ala Thr Gly Ala Leu Ala Ser Ala Val Ser Gly
 355 360 365
 Tyr Val Gln Ala Leu Ala Ser Ala Gly Val Val Ala Val Leu Ala Leu
 370 375 380
 Gly Ala Pro Ala Pro Gln Gly Cys Ala Val Ala Leu Ala Ser Asp Arg
 385 390 395 400
 Cys Ser Ile His Leu Gln Leu Gln Gly Leu Val Asp Pro Ala Arg Glu
 405 410 415
 Leu Gly Lys Leu Gln Ala Lys Arg Val Glu Ala Gln Arg Gln Ala Gln
 420 425 430
 Arg Leu Arg Glu Arg Arg Ala Ala Ser Gly Tyr Pro Val Lys Val Pro
 435 440 445
 Leu Glu Val Gln Glu Ala Asp Glu Ala Lys Leu Gln Gln Thr Glu Ala
 450 455 460
 Glu Leu Arg Lys Val Asp Glu Ala Ile Ala Leu Phe Gln Lys Met Leu
 465 470 475 480

<210> 560

517

<211> 96

<212> PRT

<213> Homo sapiens

<400> 560

Ala Cys Leu Glu Arg Cys Gly Ser Trp Arg Pro His Arg Pro Met Thr
 1 5 10 15

Ser Gly Ala Arg Glu Asn Pro Ile Gln Val Pro Arg Ser Ser Leu Glu
 20 25 30

Ala Thr Gly Ala Gln Glu Arg Trp Ala Glu Asp Val Pro Tyr Pro Thr
 35 40 45

Thr Arg Ala Val Ser Leu Pro Pro Ser Leu Gly Val Gly Ser Thr Gly
 50 55 60

Met Ser Ser Ser Arg Phe Leu Gly Ser Leu Gly Lys His Gly Arg Leu
 65 70 75 80

Asp Ser Ser Arg Arg Ala Arg Leu Trp Gly Arg Gly Gly Arg Gly Gly
 85 90 95

<210> 561

<211> 60

<212> PRT

<213> Homo sapiens

<400> 561

Ile Arg His Glu Ser Ser Ile Leu Ser Val Leu Phe Ile Arg Phe Leu
 1 5 10 15

Lys Cys Ala Asp Pro Phe Lys Thr Pro Ala Tyr Leu Cys Asn Lys Glu
 20 25 30

Lys Tyr Ser Lys Ile Leu Pro Ser Phe Ser His Thr Val Leu Lys Met
 35 40 45

Leu Gln Asp Gln Ile Ile Ala His Lys Ile Arg Ser
 50 55 60

<210> 562

<211> 241

<212> PRT

518

<213> Homo sapiens

<400> 562

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Ser Ser Met Ala Lys Pro Cys Gly Val Arg Leu Ser Gly Glu Ala Arg
 1           5           10           15

Lys Gln Val Glu Val Phe Arg Gln Asn Leu Phe Gln Glu Ala Glu Glu
      20           25           30

Phe Leu Tyr Arg Phe Leu Pro Gln Lys Ile Ile Tyr Leu Asn Gln Leu
 35           40           45

Leu Gln Glu Asp Ser Leu Asn Val Ala Asp Leu Thr Ser Leu Arg Ala
 50           55           60

Pro Leu Asp Ile Pro Ile Pro Asp Pro Pro Pro Lys Asp Asp Glu Met
 65           70           75           80

Glu Thr Asp Lys Gln Glu Lys Lys Glu Val Pro Lys Cys Gly Phe Leu
      85           90           95

Pro Gly Asn Glu Lys Val Leu Ser Leu Leu Ala Leu Val Lys Pro Glu
      100           105           110

Val Trp Thr Leu Lys Glu Lys Cys Ile Leu Val Ile Thr Trp Ile Gln
      115           120           125

His Leu Ile Pro Lys Ile Glu Asp Gly Asn Asp Phe Gly Val Ala Ile
      130           135           140

Gln Glu Lys Val Leu Glu Arg Val Asn Ala Val Lys Thr Lys Val Glu
      145           150           155           160

Ala Phe Gln Thr Thr Ile Ser Lys Tyr Phe Ser Glu Arg Gly Asp Ala
      165           170           175

Val Ala Lys Ala Ser Lys Glu Thr His Val Met Asp Tyr Arg Ala Leu
      180           185           190

Val His Glu Arg Asp Glu Ala Ala Tyr Gly Glu Leu Arg Ala Met Val
      195           200           205

Leu Asp Leu Arg Ala Phe Tyr Ala Glu Leu Tyr His Ile Ile Ser Ser
      210           215           220

Asn Leu Glu Lys Ile Val Asn Pro Lys Gly Glu Glu Lys Pro Ser Met
      225           230           235           240

Tyr

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519

<210> 563
 <211> 200
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (145)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 563
 Leu Gly Ser Ile Gln Val Met Gln Ala Val Arg Asn Ala Gly Ser Arg
 1 5 10 15
 Phe Leu Arg Ser Trp Thr Trp Pro Gln Thr Ala Gly Arg Val Val Ala
 20 25 30
 Arg Thr Pro Ala Gly Thr Ile Cys Thr Gly Ala Arg Gln Leu Gln Asp
 35 40 45
 Ala Ala Ala Lys Gln Lys Val Glu Gln Asn Ala Ala Pro Ser His Thr
 50 55 60
 Lys Phe Ser Ile Tyr Pro Pro Ile Pro Gly Glu Glu Ser Ser Leu Arg
 65 70 75 80
 Trp Ala Gly Lys Lys Phe Glu Glu Ile Pro Ile Ala His Ile Lys Ala
 85 90 95
 Ser His Asn Asn Thr Gln Ile Gln Val Val Ser Ala Ser Asn Glu Pro
 100 105 110
 Leu Ala Phe Ala Ser Cys Gly Thr Glu Gly Phe Arg Asn Ala Lys Lys
 115 120 125
 Gly Thr Gly Ile Ala Ala Gln Thr Ala Gly Ile Ala Ala Ala Ala Arg
 130 135 140
 Xaa Lys Gln Lys Gly Val Ile His Ile Arg Val Val Val Lys Gly Leu
 145 150 155 160
 Gly Pro Gly Arg Leu Ser Ala Met His Gly Leu Ile Met Gly Gly Leu
 165 170 175
 Glu Val Ile Ser Ile Thr Asp Asn Thr Pro Ile Pro His Asn Gly Cys
 180 185 190
 Arg Pro Arg Lys Ala Arg Lys Leu
 195 200

520

<210> 564

<211> 115

<212> PRT

<213> Homo sapiens

<400> 564

Val Arg Leu Val Pro Gly Ala Asp Lys Tyr Asn Asp Asp Ile Arg Lys
 1 5 10 15

Gly Ile Val Leu Leu Glu Glu Leu Leu Pro Lys Gly Ser Lys Glu Glu
 20 25 30

Gln Arg Asp Tyr Val Phe Tyr Leu Ala Val Gly Asn Tyr Arg Leu Lys
 35 40 45

Glu Tyr Glu Lys Ala Leu Lys Tyr Val Arg Gly Leu Leu Gln Thr Glu
 50 55 60

Pro Gln Asn Asn Gln Ala Lys Glu Leu Glu Arg Leu Ile Asp Lys Ala
 65 70 75 80

Met Lys Lys Asp Gly Leu Val Gly Met Ala Ile Val Gly Gly Met Ala
 85 90 95

Leu Gly Val Ala Gly Leu Ala Gly Leu Ile Gly Leu Ala Val Ser Lys
 100 105 110

Ser Lys Ser
 115

<210> 565

<211> 101

<212> PRT

<213> Homo sapiens

<400> 565

Pro Thr Arg Pro Asp Glu His Asp Glu Asn Asn Ala Glu Ala Ser Ala
 1 5 10 15

Glu Leu Ser Asn Glu Gly Val Met Asn His Arg Ser Glu Glu Glu Arg
 20 25 30

Val Thr Glu Thr Gln Lys Asn Glu Arg Val Lys Lys Gln Leu Gln Ala
 35 40 45

Leu Ser Ser Glu Leu Ala Gln Ala Arg Asp Glu Thr Lys Lys Thr Gln

521

50 55 60
 Asn Asp Val Leu His Ala Glu Asn Val Lys Ala Gly Arg Asp Lys Tyr
 65 70 75 80
 Lys Thr Leu Arg Gln Ile Arg Gln Gly Asn Thr Lys Gln Arg Ile Asp
 85 90 95
 Glu Phe Glu Ala Met
 100

<210> 566
 <211> 25
 <212> PRT
 <213> Homo sapiens

<400> 566
 Thr Ala Asp Leu Val Ile Arg Pro Pro Arg Pro Leu Lys Val Leu Gly
 1 5 10 15
 Phe Cys Val Phe Cys Ala Pro Pro Leu
 20 25

<210> 567
 <211> 274
 <212> PRT
 <213> Homo sapiens

<220>
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 <222> (182)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (216)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (222)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (224)
 <223> Xaa equals any of the naturally occurring L-amino acids

522

<220>

<221> SITE

<222> (228)

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<222> (228)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>

<221> SITE

 $\langle 222 \rangle$ (231)

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<222> (231)
<223> xaa equals any of the naturally occurring L-amino acids
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<400> 567

<400> 567
Ala Ser Pro Glu Val Glu Ala Gly Ala Ala Arg Gln Pro Leu Leu Gly
1 5 10 15

Val Ala Gly Gly Gln Thr Leu Gly Ala Thr Pro Gly Pro Val Met Asn
20 25 30

Gly Pro Ala Asp Gly Glu Val Asp Tyr Lys Lys Lys Tyr Arg Asn Leu
35 40 45

Lys Arg Lys Leu Lys Phe Leu Ile Tyr Glu His Glu Cys Phe Gln Glu
50 55 60

Glu Leu Arg Lys Ala Gln Arg Lys Leu Leu Lys Val Ser Arg Asp Lys
65 70 75 80

Ser Phe Leu Leu Asp Arg Leu Leu Gln Tyr Glu Asn Val Asp Glu Asp
85 90 95

Ser Ser Asp Ser Asp Ala Thr Ala Ser Ser Asp Asn Ser Glu Thr Glu
100 105 110

Gly Thr Pro Lys Leu Ser Asp Thr Pro Ala Pro Lys Arg Lys Arg Ser
115 120 125

Pro Pro Leu Gly Gly Ala Pro Ser Pro Ser Ser Leu Ser Leu Pro Pro
130 135 140

Ser Thr Gly Phe Pro Leu Gln Ala Ser Gly Val Pro Ser Pro Tyr Leu
145 150 155 160

Ser Ser Leu Ala Ser Ser Arg Tyr Pro Pro Phe Pro Ser Asp Tyr Leu
165 170 175

Ala Leu Gln Leu Pro Xaa Pro Ser Pro Leu Arg Pro Lys Arg Glu Lys
180 185 190

Arg Pro Arg Leu Pro Arg Lys Leu Lys Met Ala Val Gly Pro Pro Asp
195 200 205

523

Cys Pro Val Gly Gly Pro Leu Xaa Phe Pro Gly Arg Gly Xaa Gly Xaa
 210 215 220
 Gly Val Gly Xaa Thr Leu Xaa Pro Leu Pro Pro Pro Lys Met Pro Pro
 225 230 235 240
 Pro Thr Ile Leu Ser Thr Val Pro Arg Gln Met Phe Ser Asp Ala Gly
 245 250 255
 Ser Gly Asp Asp Ala Leu Asp Gly Asp Asp Asp Leu Val Ile Asp Ile
 260 265 270
 Pro Glu

<210> 568

<211> 133

<212> PRT

<213> Homo sapiens

<220>

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<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 568

Ala Arg Gly Asp His Val Arg Ser Arg Glu Thr Gly Arg Gln Ser Ala
 1 5 10 15
 Ser Lys Gly Gln Ile Pro Leu Leu Pro Arg Gly Pro Ala Val Pro Gly
 20 25 30
 Gly Pro Ser Ala Gln Thr Ala Ala Gln Arg Glu Leu Arg Gly Xaa Val
 35 40 45
 Gly Ala Gly Ala Pro Val Tyr Leu Ala Ala Val Leu Glu Tyr Leu Thr
 50 55 60
 Ala Glu Ile Leu Glu Leu Ala Gly Asn Ala Ala Arg Asp Asn Lys Lys
 65 70 75 80
 Thr Arg Ile Ile Pro Arg His Leu Gln Leu Ala Ile Arg Asn Asp Glu
 85 90 95
 Glu Leu Asn Lys Leu Leu Gly Lys Val Thr Ile Ala Gln Gly Gly Val
 100 105 110
 Leu Pro Asn Ile Gln Ala Val Leu Leu Pro Lys Lys Thr Glu Ser Gln
 115 120 125

524

Lys Thr Lys Ser Lys
130

<210> 569
<211> 153
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (136)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
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<222> (137)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (152)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 569
Met Cys Arg Gly Tyr Ala Trp Asn Pro Gly Ile Thr Leu Gln Asn Arg
1 5 10 15

Lys Thr Lys Glu Gly Pro Arg Ala Pro Pro Ser Arg Met Pro Glu Pro
20 25 30

Ala Gly Gly Leu Arg Gly Cys Glu Ala Val Gly Thr Leu Leu Met Lys
35 40 45

Glu Thr Val Phe Ala Leu His Pro Ser Leu Pro Leu Gly Ala Gly Ser
50 55 60

Ser Pro Ser Ala Thr Cys Ser Glu Gly Leu His Leu Arg Gly Glu Gly
65 70 75 80

Trp Gly Lys Ser Pro Pro Val Pro Phe Leu Trp Pro Cys Cys Pro His
85 90 95

Thr Gln Leu Arg Gly Pro Thr Leu Gly Lys Ala Gly Ser Ala Arg Ser
100 105 110

Leu Ser Pro Ile Ser Ala Leu Ser Ala Trp Ile Pro Ala Glu Ala Met
115 120 125

525

Lys Gly Asn Lys Glu Lys Arg Xaa Xaa Lys Lys Lys Lys Lys Lys Lys
 130 135 140

Lys Lys Lys Lys Lys Lys Lys Xaa Pro
 145 150

<210> 570

<211> 327

<212> PRT

<213> Homo sapiens

<400> 570

Pro Gly Ser Pro Arg Arg Cys Asp Ile Ile Ile Ile Ser Gly Arg Lys
 1 5 10 15

Glu Lys Cys Glu Ala Ala Lys Glu Ala Leu Glu Ala Leu Val Pro Val
 20 25 30

Thr Ile Glu Val Glu Val Pro Phe Asp Leu His Arg Tyr Val Ile Gly
 35 40 45

Gln Lys Gly Ser Gly Ile Arg Lys Met Met Asp Glu Phe Glu Val Asn
 50 55 60

Ile His Val Pro Ala Pro Glu Leu Gln Ser Asp Ile Ile Ala Ile Thr
 65 70 75 80

Gly Leu Ala Ala Asn Leu Asp Arg Ala Lys Ala Gly Leu Leu Glu Arg
 85 90 95

Val Lys Glu Leu Gln Ala Glu Gln Glu Asp Arg Ala Leu Arg Ser Phe
 100 105 110

Lys Leu Ser Val Thr Val Asp Pro Lys Tyr His Pro Lys Ile Ile Gly
 115 120 125

Arg Lys Gly Ala Val Ile Thr Gln Ile Arg Leu Glu His Asp Val Asn
 130 135 140

Ile Gln Phe Pro Asp Lys Asp Asp Gly Asn Gln Pro Gln Asp Gln Ile
 145 150 155 160

Thr Ile Thr Gly Tyr Glu Lys Asn Thr Glu Ala Ala Arg Asp Ala Ile
 165 170 175

Leu Arg Ile Val Gly Glu Leu Glu Gln Met Val Ser Glu Asp Val Pro
 180 185 190

Leu Asp His Arg Val His Ala Arg Ile Ile Gly Ala Arg Gly Lys Ala

526

195	200	205
Ile Arg Lys Ile Met Asp Glu Phe Lys Val Asp Ile Arg Phe Pro Gln		
210	215	220
Ser Gly Ala Pro Asp Pro Asn Cys Val Thr Val Thr Gly Leu Pro Glu		
225	230	235 240
Asn Val Glu Glu Ala Ile Asp His Ile Leu Asn Leu Glu Glu Glu Tyr		
245	250	255
Leu Ala Asp Val Val Asp Ser Glu Ala Leu Gln Val Tyr Met Lys Pro		
260	265	270
Pro Ala His Glu Glu Ala Lys Ala Pro Ser Arg Gly Phe Val Val Arg		
275	280	285
Asp Ala Pro Trp Thr Ala Ser Ser Ser Glu Lys Ala Pro Asp Met Ser		
290	295	300
Ser Ser Glu Glu Phe Pro Ser Phe Gly Ala Gln Val Ala Pro Lys Thr		
305	310	315 320
Leu Pro Trp Gly Pro Lys Arg		
325		

<210> 571

<211> 166

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (12)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 571

Gly Asn Ser Arg Val Asp Pro Arg Xaa Arg Gly Xaa Ala His Thr Cys
1 5 10 15

Ala Pro Cys Pro Ala Pro Gly Pro Leu Ala Gly Arg Ala Val Ser Gly
20 25 30

His Gly Ser Leu Pro Pro Asp Arg Arg Ala Pro Ser Ala Leu Ser Ser

527

35 40 45
 Pro Ala Asp Glu Gly Glu Arg Arg Arg Pro Asp Leu Asp Glu Ile His
 50 55 60
 Arg Glu Leu Arg Pro Gln Gly Ser Ala Arg Pro Gln Pro Asp Pro Asn
 65 70 75 80
 Ala Glu Phe Asp Pro Asp Leu Pro Gly Gly Gly Leu His Arg Cys Leu
 85 90 95
 Ala Cys Ala Arg Tyr Phe Ile Asp Ser Thr Asn Leu Lys Thr His Phe
 100 105 110
 Arg Ser Lys Asp His Lys Lys Arg Leu Lys Gln Leu Ser Val Glu Pro
 115 120 125
 Tyr Ser Gln Glu Glu Ala Glu Arg Ala Ala Gly Met Gly Ser Tyr Val
 130 135 140
 Pro Pro Arg Arg Leu Ala Val Pro Thr Glu Val Ser Thr Glu Val Pro
 145 150 155 160
 Glu Met Asp Thr Ser Thr
 165

<210> 572

<211> 113

<212> PRT

<213> Homo sapiens

<400> 572

Gln Ser Ser Thr Phe His Pro Ala Pro Ala Phe Gly Ala Thr Val Ala
 1 5 10 15
 Ala Phe His Arg Arg Ala Ala Leu Arg Ala Pro Glu Pro Ala Met Ser
 20 25 30
 Gly Pro Asn Gly Asp Leu Gly Met Pro Val Glu Ala Gly Ala Glu Gly
 35 40 45
 Glu Glu Asp Gly Phe Gly Glu Ala Glu Tyr Ala Ala Ile Asn Ser Met
 50 55 60
 Leu Asp Gln Ile Asn Ser Cys Leu Asp His Leu Glu Glu Lys Asn Asp
 65 70 75 80
 His Leu His Ala Arg Leu Gln Glu Leu Leu Glu Ser Asn Arg Gln Thr
 85 90 95

528

Arg Leu Glu Phe Gln Gln Gln Leu Gly Glu Ala Pro Ser Asp Ala Ser
 100 105 110

Pro

<210> 573

<211> 99

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (37)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (38)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 573

Gly Ser Gly Ser Ser Arg Asp Leu His Lys Ala Leu Trp Glu Ala Gly
 1 5 10 15

Trp Glu Thr Val Glu Gly Gly Cys Pro Leu Xaa Pro Arg Arg His Arg
 20 25 30

Ile Trp Ala Leu Xaa Xaa Ala Phe Leu Pro Glu Tyr Ala Ala Ile Asn
 35 40 45

Ser Met Leu Asp Gln Ile Asn Ser Cys Leu Asp His Leu Glu Glu Lys
 50 55 60

Asn Asp His Leu His Ala Arg Leu Gln Glu Leu Leu Glu Ser Asn Arg
 65 70 75 80

Gln Thr Arg Leu Glu Phe Gln Gln Gln Leu Gly Glu Ala Pro Ser Asp
 85 90 95

Ala Ser Pro

529

<210> 574
 <211> 197
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (97)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (124)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (129)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 574
 Arg Trp Ala Arg Val Glu Ala Ala Val Met Glu Gly Ala Gly Ala Gly
 1 5 10 15

Ser Gly Phe Arg Lys Glu Leu Val Ser Arg Leu Leu His Leu His Phe
 20 25 30

Lys Asp Asp Lys Thr Lys Val Ser Gly Asp Ala Leu Gln Leu Met Val
 35 40 45

Glu Leu Leu Lys Val Phe Val Val Glu Ala Ala Val Arg Gly Val Arg
 50 55 60

Gln Ala Gln Ala Glu Asp Ala Leu Arg Val Asp Val Asp Gln Leu Glu
 65 70 75 80

Lys Val Leu Arg Ser Cys Ser Gly Leu Leu Gly Ile Ser Ala Val Ala
 85 90 95

Xaa Ala Thr Pro Arg Gly Ala Pro Gly Pro Gln Lys Gln Ala Leu Cys
 100 105 110

Phe Gln Arg Pro Leu Ile Arg Gly Arg Glu Gly Xaa Glu Gly Phe Gly
 115 120 125

Xaa Asp Ser Asn Lys Ile Ser Gly Ser Leu Gln Pro Val Gln Lys Gly
 130 135 140

Gln Asp Cys Ser Ala Leu Arg Ala Leu Glu Cys Pro Val Gly Thr Leu

530

145 150 155 160
 Val Trp Glu Gly Ala Ala Pro Gly Glu Ser Leu Pro Leu Leu Pro Gly
 165 170 175
 Thr Ile Val Cys Met Pro Pro Gly Val Leu Gln Ala Gly Ala Gly Lys
 180 185 190
 Gly Leu Ala Ser Arg
 195

<210> 575
 <211> 47
 <212> PRT
 <213> Homo sapiens

<400> 575
 Leu Pro Met Val Asp Leu Met Glu Lys Leu Asn Ile Phe His Tyr Ala
 1 5 10 15
 Leu Gln Asn Thr Val Tyr Val Ser Ala Ser Leu Gly Asn Gly Arg Gly
 20 25 30
 Gln Lys Lys Val Thr Phe Asn Leu Cys Ile Phe Ala Lys Pro Tyr
 35 40 45

<210> 576
 <211> 115
 <212> PRT
 <213> Homo sapiens

<400> 576
 Trp Ser Arg Thr Ser Gln Pro Leu Pro Ser Thr Val Gly Cys Pro Arg
 1 5 10 15
 Arg Arg Gly Phe Lys Asp Phe Gln Arg Arg Ile Leu Val Ala Thr Asn
 20 25 30
 Leu Phe Gly Arg Gly Met Asp Ile Glu Arg Val Asn Ile Ala Phe Asn
 35 40 45
 Tyr Asp Met Pro Glu Asp Ser Asp Thr Tyr Leu His Arg Val Ala Arg
 50 55 60
 Ala Gly Arg Phe Gly Thr Lys Gly Leu Ala Ile Thr Phe Val Ser Asp
 65 70 75 80

531

Glu Asn Asp Ala Lys Ile Leu Asn Asp Val Gln Asp Arg Phe Glu Val
 85 90 95

Asn Ile Ser Glu Leu Pro Asp Glu Ile Asp Ile Ser Ser Tyr Ile Glu
 100 105 110

Gln Thr Arg
 115

<210> 577

<211> 346

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (37)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 577

Val Thr Ser Cys Val Ala Leu Leu Pro Ala Arg Arg Met Thr Tyr Thr
 1 5 10 15

Thr Glu Thr Ala Leu Leu Asn Trp Ser Thr Cys Gln Met Val Leu Arg
 20 25 30

Gly Ala Glu Thr Xaa Gly Cys Val Ile Val Ser Ala Ala Lys Ala Gln
 35 40 45

Leu Leu Gln Cys Gln His His Pro Ala Trp Tyr Gly Asp Thr Leu Lys
 50 55 60

Gln Lys Thr Ser Trp Thr Cys Leu Leu Asp Gly Met Gln Tyr Phe Ala
 65 70 75 80

Thr Thr Glu Ser Ser Pro Thr Glu Gln Asp Gly Arg Gln Leu Trp Leu
 85 90 95

Glu Val Lys Asn Ile Glu Glu His Arg Gln Arg Ser Leu Asp Ser Val
 100 105 110

Gln Glu Leu Met Glu Ser Gly Gln Ala Val Gly Gly Met Val Thr Thr
 115 120 125

Thr Thr Asp Trp Asn Gln Pro Ala Glu Ala Gln Gln Ala Gln Gln Val
 130 135 140

Gln Arg Ile Ile Ser Arg Cys Asn Cys Arg Met Tyr Tyr Ile Ser Tyr
 145 150 155 160

532

Ser His Asp Ile Asp Pro Glu Leu Ala Thr Gln Ile Lys Pro Pro Glu
 165 170 175

Val Leu Glu Asn Gln Glu Lys Glu Asp Leu Leu Lys Lys Gln Glu Gly
 180 185 190

Ala Val Asp Thr Phe Thr Leu Ile His His Glu Leu Glu Ile Ser Thr
 195 200 205

Asn Pro Ala Gln Tyr Ala Met Ile Leu Asp Ile Val Asn Asn Leu Leu
 210 215 220

Leu His Val Glu Pro Lys Arg Lys Glu His Ser Glu Lys Lys Gln Arg
 225 230 235 240

Val Arg Phe Gln Leu Glu Ile Ser Ser Asn Pro Glu Glu Gln Arg Ser
 245 250 255

Ser Ile Leu His Leu Gln Glu Ala Val Arg Gln His Val Ala Gln Ile
 260 265 270

Arg Gln Leu Glu Lys Gln Met Tyr Ser Ile Met Lys Ser Leu Gln Asp
 275 280 285

Asp Ser Lys Asn Glu Asn Leu Leu Asp Leu Asn Gln Lys Leu Gln Leu
 290 295 300

Gln Leu Asn Gln Glu Lys Ala Asn Leu Gln Leu Glu Ser Glu Glu Leu
 305 310 315 320

Asn Ile Leu Ile Arg Cys Phe Lys Asp Phe Gln Leu Gln Arg Ala Asn
 325 330 335

Lys Met Glu Leu Arg Lys His Lys Lys Met
 340 345

<210> 578

<211> 91

<212> PRT

<213> Homo sapiens

<400> 578

Arg His Glu Gly His Leu Gly Ser Gly Arg Asn Gly Gly Gly Ser Met
 1 5 10 15

Asn Ala Pro Pro Ala Phe Glu Ser Phe Leu Leu Phe Glu Gly Glu Lys
 20 25 30

533

Ile Thr Ile Asn Lys Asp Thr Lys Val Pro Asn Ala Cys Leu Phe Thr
35 40 45

Ile Asn Lys Glu Asp His Thr Leu Gly Asn Ile Ile Lys Ser Arg Ala
50 55 60

Cys Phe Pro Phe Ala Phe Cys Arg Asp Cys Gln Phe Pro Glu Ala Ser
65 70 75 80

Pro Ala Thr Leu Pro Val Gln Pro Ala Glu Leu
85 90

<210> 579

<211> 331

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (18)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (20)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (300)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (311)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (313)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (320)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

534

<222> (325)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 579

Gly Arg Pro Thr Arg Pro Gly Gly Leu Gly Ser Gly Val Leu Ala Leu
 1 5 10 15

Ala Xaa Gly Xaa Pro Ala Arg Leu Ala Gly Thr Val His Glu Val Gly
 20 25 30

Asp Ala Pro Arg Arg Ala Pro Asp Gln Ala Ala Glu Ile Gly Ser Arg
 35 40 45

Gly Ser Thr Lys Ala Gln Gly Pro Gln Gln Gln Pro Gly Ser Glu Gly
 50 55 60

Pro Ser Tyr Ala Lys Lys Val Ala Leu Trp Leu Ala Gly Leu Leu Gly
 65 70 75 80

Ala Gly Gly Thr Val Ser Val Val Tyr Ile Phe Gly Asn Asn Pro Val
 85 90 95

Asp Glu Asn Gly Ala Lys Ile Pro Asp Glu Phe Asp Asn Asp Pro Ile
 100 105 110

Leu Val Gln Gln Leu Arg Arg Thr Tyr Lys Tyr Phe Lys Asp Tyr Arg
 115 120 125

Gln Met Ile Ile Glu Pro Thr Ser Pro Cys Leu Leu Pro Asp Pro Leu
 130 135 140

Gln Glu Pro Tyr Tyr Gln Pro Pro Tyr Thr Leu Val Leu Glu Leu Thr
 145 150 155 160

Gly Val Leu Leu His Pro Glu Trp Ser Leu Ala Thr Gly Trp Arg Phe
 165 170 175

Lys Lys Arg Pro Gly Ile Glu Thr Leu Phe Gln Gln Leu Ala Pro Leu
 180 185 190

Tyr Glu Ile Val Ile Phe Thr Ser Glu Thr Gly Met Thr Ala Phe Pro
 195 200 205

Leu Ile Asp Ser Val Asp Pro His Gly Phe Ile Ser Tyr Arg Leu Phe
 210 215 220

Arg Asp Ala Thr Arg Tyr Met Asp Gly His His Val Lys Asp Ile Ser
 225 230 235 240

Cys Leu Asn Arg Asp Pro Ala Arg Val Val Val Val Asp Cys Lys Lys
 245 250 255

535

Glu Ala Phe Arg Leu Gln Pro Tyr Asn Gly Val Ala Leu Arg Pro Trp
260 265 270

Asp Gly Asn Ser Asp Asp Arg Val Leu Leu Asp Leu Ser Ala Phe Leu
275 280 285

Lys Thr Ile Ala Leu Asn Gly Val Gly Gly Arg Xaa Glu Pro Cys Trp
290 295 300

Glu His Tyr Ala Leu Gly Xaa Asp Xaa Pro Arg Trp Ala Ala Phe Xaa
305 310 315 320

Asn Ser Gly Lys Xaa Gly Leu Glu Ala Gly Arg
325 330

<210> 580

<211> 374

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (235)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (285)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (307)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (319)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (324)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (341)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (359)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 580

Pro Ser Thr Val Arg Asn Ser Arg Val Asp Pro Arg Val Arg Pro Arg
1 5 10 15

Val Arg Ala Gly Val Ala Ala Leu Ala Thr Val Gly Val Ala Ser Gly
20 25 30

Pro Gly Pro Gly Arg Pro Gly Pro Leu Gln Asp Glu Thr Leu Gly Val
35 40 45

Ala Ser Val Pro Ser Gln Trp Arg Ala Val Gln Gly Ile Arg Gly Glu
50 55 60

Thr Lys Ser Cys Gln Thr Ala Ser Ile Ala Thr Ala Ser Ala Ser Ala
65 70 75 80

Gln Ala Arg Asn His Val Asp Ala Gln Val Gln Thr Glu Ala Pro Val
85 90 95

Pro Val Ser Val Gln Pro Pro Ser Gln Tyr Asp Ile Pro Arg Leu Ala
100 105 110

Ala Phe Leu Arg Arg Val Glu Ala Met Val Ile Arg Glu Leu Asn Lys
115 120 125

Asn Trp Gln Ser His Ala Phe Asp Gly Phe Glu Val Asn Trp Thr Glu
130 135 140

Gln Gln Gln Met Val Ser Cys Leu Tyr Thr Leu Gly Tyr Pro Pro Ala
145 150 155 160

Gln Ala Gln Gly Leu His Val Thr Ser Ile Ser Trp Asn Ser Thr Gly
165 170 175

Ser Val Val Ala Cys Ala Tyr Gly Arg Leu Asp His Gly Asp Trp Ser
180 185 190

Thr Leu Lys Ser Phe Val Cys Ala Trp Asn Leu Asp Arg Arg Asp Leu
195 200 205

Arg Pro Gln Gln Pro Ser Ala Val Val Glu Val Pro Ser Ala Val Leu
210 215 220

Cys Leu Ala Phe His Pro Thr Gln Pro Ser Xaa Val Ala Gly Gly Leu

537

225 230 235 240
 Tyr Ser Gly Glu Val Leu Val Trp Asp Leu Ser Arg Leu Glu Asp Pro
 245 250 255
 Leu Leu Trp Arg Thr Gly Leu Thr Asp Asp Thr His Thr Asp Pro Val
 260 265 270
 Ser Gln Val Val Trp Leu Pro Glu Pro Gly His Ser Xaa Arg Phe Gln
 275 280 285
 Val Leu Ser Val Ala Thr Asp Gly Lys Val Leu Leu Trp Gln Gly Ile
 290 295 300
 Gly Val Xaa Gln Leu Gln Phe Thr Glu Gly Phe Ala Trp Phe Xaa Gln
 305 310 315 320
 Gln Leu Pro Xaa Ser Thr Lys Leu Lys Lys His Pro Arg Gly Arg Pro
 325 330 335
 Arg Trp Ala Pro Xaa Gln Ala Phe Phe Gln Phe Asp Leu Arg Phe Ser
 340 345 350
 Phe Trp Gln Glu Ala Val Xaa Val Gln Phe Ser Trp His Trp Arg Ala
 355 360 365
 Ala Leu Arg Gly Ala His
 370

<210> 581

<211> 94

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (90)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 581

Cys Pro Asp Gln Asn Gly Trp Ala Ser Phe Gly Ala Pro Leu Ser Ala
 1 5 10 15

Gly Gly Gln Pro Cys Tyr Leu Leu Asp Ile Gly Cys Gly Ser Gly Leu

538

[illegible]

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<210> 582
<211> 163
<212> PRT
<213> Homo sapiens
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<400> 582
Pro Thr Arg Pro Ala Ala Gly Gly Ala Glu Arg Ile Ala Gly Ser Ala
  1             5             10             15
Met Ser Ser Glu Pro Pro Pro Pro Pro Gln Pro Pro Thr His Gln Ala
      20             25             30
Ser Val Gly Leu Leu Asp Thr Pro Arg Ser Arg Glu Arg Ser Pro Ser
      35             40             45
Pro Leu Arg Gly Asn Val Val Pro Ser Pro Leu Pro Thr Arg Arg Thr
      50             55             60
Arg Thr Phe Ser Ala Thr Val Arg Ala Ser Gln Gly Pro Val Tyr Lys
      65             70             75             80
Gly Val Cys Lys Cys Phe Cys Arg Ser Lys Gly His Gly Phe Ile Thr
      85             90             95
Pro Ala Asp Gly Gly Pro Asp Ile Phe Leu His Ile Ser Asp Val Glu
      100            105            110
Gly Glu Tyr Val Pro Val Glu Gly Asp Glu Val Thr Tyr Lys Met Cys
      115            120            125
Ser Ile Pro Pro Lys Asn Glu Lys Leu Gln Ala Val Glu Val Val Ile
      130            135            140
Thr His Leu Ala Pro Gly Thr Lys His Glu Thr Trp Ser Gly His Val
      145            150            155            160

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Ile Ser Ser

<210> 583
 <211> 293
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (52)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (53)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (58)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (150)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (171)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (207)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (254)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 583
 Leu Leu Gly Pro Asn Leu Thr Met Gly Ser Gln Pro Gly Arg Ile Pro
 1 5 10 15

Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr

540

	20		25		30
Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met Ile Asp Ser Glu	35	40	45		
Cys Arg Pro Xaa Xaa Arg Glu Leu Val Xaa Glu Phe Ser Arg Met Ala	50	55	60		
Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu Asp Leu Gly Pro	65	70	75	80	
Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu Leu Glu Asp Asp	85	90	95		
Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu Val Pro Gln Gln	100	105	110		
Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly Gly Met Val His	115	120	125		
His Arg His Arg Ser Ser Ser Thr Arg Ser Gly Gly Gly Asp Leu Thr	130	135	140		
Leu Gly Leu Glu Pro Xaa Glu Arg Gly Gly Pro Gln Val Ser Thr Gly	145	150	155	160	
Thr Leu Arg Arg Ala Gly Ser Asp Val Phe Xaa Gly Asp Leu Gly Met	165	170	175		
Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His Asp Pro Ser Pro	180	185	190		
Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu Pro Ser Xaa Thr	195	200	205		
Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln Pro Glu Tyr Val	210	215	220		
Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro Arg Glu Gly Pro	225	230	235	240	
Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu Arg Xaa Lys Thr	245	250	255		
Leu Ser Pro Gly Lys Asn Gly Val Val Lys Glu Phe Leu Pro Leu Gly	260	265	270		
Val Pro Trp Arg Thr Pro Ser Ile Asp Thr Pro Gly Glu Gly Ala Cys	275	280	285		
Pro Ser Ala Pro Pro					

541

290

<210> 584

<211> 132

<212> PRT

<213> Homo sapiens

<400> 584

Gly Gly Ala Gln Pro Gly Met Glu Gly Ala Ala Ala Thr Val His Leu
 1 5 10 15

Ile Ser Gln Trp Ala Val Glu Pro Asn Ala Arg Val Gly Pro Leu Leu
 20 25 30

Glu Val Glu Ala Ala Ala Ala Asp His His Glu Ala Ala Ala Gly Ala
 35 40 45

Gly Ser Ala Val Glu Lys Ile Cys Ile Asp Lys Gly Leu Thr Asp Glu
 50 55 60

Ser Glu Ile Leu Arg Phe Leu Gln His Gly Thr Leu Val Gly Leu Leu
 65 70 75 80

Pro Val Pro His Pro Ile Leu Ile Arg Lys Tyr Gln Ala Asn Ser Gly
 85 90 95

Thr Ala Met Trp Phe Arg Thr Tyr Met Trp Gly Val Ile Tyr Leu Arg
 100 105 110

Asn Val Asp Pro Pro Val Trp Tyr Asp Thr Asp Val Lys Leu Phe Glu
 115 120 125

Ile Gln Arg Val
 130

<210> 585

<211> 218

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (54)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (92)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (117)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

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<222> (140)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

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<222> (141)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (188)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (199)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (200)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 585

Arg	Glu	Arg	Cys	Arg	Arg	Glu	Ala	Leu	Arg	Gly	Ser	Arg	Leu	Cys	Pro
1				5					10					15	

Ala	Thr	Pro	Pro	Ser	Ala	Leu	Gly	Ser	Gln	Asp	Gly	Ser	Arg	Thr	Arg
				20				25					30		

Asp	Arg	Leu	Gly	Ala	Ala	Gly	Trp	Pro	Gly	Leu	Val	Val	Gly	Leu	Cys
		35					40					45			

Thr	Pro	Ala	Ala	Gly	Xaa	Gln	Arg	Asp	Leu	Leu	His	Arg	Arg	Gly	Gly
		50				55					60				

Thr	Ala	Ser	Phe	Gly	Lys	Ser	Phe	Ala	Gln	Lys	Ser	Gly	Tyr	Phe	Leu
	65				70					75					80

Cys	Leu	Ser	Ser	Leu	Gly	Ser	Leu	Glu	Asn	Pro	Xaa	Glu	Asn	Val	Val
				85					90					95	

543

Ala Asp Ile Gln Ile Val Val Asp Lys Ser Pro Leu Pro Leu Gly Phe
 100 105 110

Ser Pro Val Cys Xaa Pro Met Asp Ser Lys Ala Ser Val Ser Lys Lys
 115 120 125

Lys Arg Met Cys Val Lys Leu Leu Pro Leu Gly Xaa Xaa Asp Thr Ala
 130 135 140

Val Phe Asp Val Arg Leu Ser Gly Lys Thr Lys Thr Val Pro Gly Tyr
 145 150 155 160

Leu Arg Ile Gly Asp Met Gly Gly Phe Ala Ile Trp Cys Lys Lys Gly
 165 170 175

Gln Gly Pro Glu Ala Ser Cys Pro Lys Pro Arg Xaa Pro Gln Pro Gly
 180 185 190

Thr Cys Lys Gly Phe Ser Xaa Xaa Ala Ala Ser Gln Pro Lys Leu Arg
 195 200 205

Ala Gly Leu Leu Gly Ser Arg Thr Ser Val
 210 215

<210> 586

<211> 233

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 586

Ala Arg Gly Glu Met Glu Gly Arg Gln Val Leu Glu Val Lys Met Gln
 1 5 10 15

Val Glu Tyr Met Ser Phe Ser Ala His Ala Asp Ala Lys Gly Ile Met
 20 25 30

Gln Leu Val Gly Gln Ala Glu Pro Xaa Ser Val Leu Leu Val His Gly
 35 40 45

Glu Ala Lys Lys Met Glu Phe Leu Lys Gln Lys Ile Glu Gln Glu Leu
 50 55 60

Arg Val Asn Cys Tyr Met Pro Ala Asn Gly Glu Thr Val Thr Leu Pro

544

[illegible]

<210> 587

<211> 116

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

$\langle 222 \rangle$ (100)

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<222> (100)
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 587

Gly Pro Leu Ser His His Ile Arg Ala Gln Leu Ser Lys Met Leu Leu
1 5 10 15

Ala Arg Lys Gln Ile Leu Cys Val Asn Val Lys Asn Phe Ala Val Ile
20 25 30

545

[illegible]

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<210> 588
<211> 133
<212> PRT
<213> Homo sapiens
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<400> 588
Ala Arg Ala Ala Val Gly Arg Thr Ala Gly Val Arg Thr Trp Ala Pro
 1              5              10              15

Leu Ala Met Ala Ala Lys Val Asp Leu Ser Thr Ser Thr Asp Trp Lys
      20              25              30

Glu Ala Lys Ser Phe Leu Lys Gly Leu Ser Asp Lys Gln Arg Glu Glu
      35              40              45

His Tyr Phe Cys Lys Asp Phe Val Arg Leu Lys Lys Ile Pro Thr Trp
      50              55              60

Lys Glu Met Ala Lys Gly Val Ala Val Lys Val Glu Glu Pro Arg Tyr
 65              70              75              80

Lys Lys Asp Lys Gln Leu Asn Glu Lys Ile Ser Leu Leu Arg Ser Asp
      85              90              95

Ile Thr Lys Leu Glu Val Asp Ala Ile Val Asn Ala Ala Asn Ser Ser
      100              105              110

Pro Pro Pro Arg Ser Leu Ile Lys Asp Leu Arg Cys Gly Lys Lys Lys
      115              120              125

Lys Lys Lys Lys Lys

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546

130

<210> 589

<211> 163

<212> PRT

<213> Homo sapiens

<400> 589

Arg His Arg Gly Gln Pro Leu Arg Gln Thr Arg Ala Ser Ser Ser Pro
 1 5 10 15

Gln Leu Ala Gly Arg Ser Ser Ser Val Leu Pro Ala Ala Ala Gln Pro
 20 25 30

Cys Thr Pro Thr Met Asp Val Phe Lys Lys Gly Phe Ser Ile Ala Lys
 35 40 45

Glu Gly Val Val Gly Ala Val Glu Lys Thr Lys Gln Gly Val Thr Glu
 50 55 60

Ala Ala Glu Lys Thr Lys Glu Gly Val Met Tyr Val Gly Ala Lys Thr
 65 70 75 80

Lys Glu Asn Val Val Gln Ser Val Thr Ser Val Ala Glu Lys Thr Lys
 85 90 95

Glu Gln Ala Asn Ala Val Ser Glu Ala Val Val Ser Ser Val Asn Thr
 100 105 110

Val Ala Thr Lys Thr Val Glu Glu Ala Glu Asn Ile Ala Val Thr Ser
 115 120 125

Gly Val Val Arg Lys Glu Asp Leu Arg Pro Ser Ala Pro Gln Gln Glu
 130 135 140

Gly Glu Ala Ser Lys Glu Lys Glu Glu Val Ala Glu Glu Ala Gln Ser
 145 150 155 160

Gly Gly Asp

<210> 590

<211> 59

<212> PRT

<213> Homo sapiens

<400> 590

547

Arg Ala Leu Leu Cys Leu Gly His His Pro Leu Leu Ala Gln Gly Val
 1 5 10 15
 Pro Ala Leu Ser Asp Met Arg Leu Pro Thr Leu Leu Pro Ser Ser Pro
 20 25 30
 Trp Pro Pro Leu Ala Cys Pro Pro Val Leu Leu His Gln Pro His Cys
 35 40 45
 Pro Pro Ser Ala Pro Pro Thr Leu Trp Ser Phe
 50 55

<210> 591

<211> 116

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (31)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 591

Val His Ala Glu Ala Gly Arg Leu Cys His Gly Asp Cys Pro Arg Leu
 1 5 10 15
 Cys Arg Pro Arg Gln Arg Ser Ala Pro Val Gln Val Tyr Thr Xaa Arg
 20 25 30
 Gln Ala Ala Leu His Gly Arg Pro Gln Arg Asp Pro Cys Val Gly Gly
 35 40 45
 Pro Arg Pro Leu Arg Cys Ser Arg Asp Cys Gly Gly Gly His Gln Arg
 50 55 60
 Leu Val Met Pro Gly Thr Trp Thr Gln Ala Trp Gln Arg Arg Gln Val
 65 70 75 80
 Val Asn Gly Leu Met Leu Gly Gln Ala Arg Ile His Val Asn Arg Leu
 85 90 95
 Glu Gln Ala Val Val Asn Leu Ala Pro Cys Glu Tyr Phe His Thr Cys
 100 105 110
 Cys Pro Phe Ala
 115

<210> 592
 <211> 290
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (30)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (239)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 592
 Arg Arg Ser Leu Asn Thr His Gly Ser Gly Val Ser Val Cys Leu Gln
 1 5 10 15

Ser Leu Thr Leu Leu Ala Thr Leu Cys Pro Gly Asp Gln Xaa Ser Leu
 20 25 30

Gly Leu Leu Thr Pro Cys Tyr Ser Gly Ser Glu Pro Ser Gly Thr Phe
 35 40 45

Gly Pro Val Asn Pro Ser Leu Asn Asn Thr Tyr Glu Phe Met Ser Thr
 50 55 60

Phe Phe Leu Glu Val Ser Ser Val Phe Pro Asp Phe Tyr Leu His Leu
 65 70 75 80

Gly Gly Asp Glu Val Asp Phe Thr Cys Trp Lys Ser Asn Pro Glu Ile
 85 90 95

Gln Asp Phe Met Arg Lys Lys Gly Phe Gly Glu Asp Phe Lys Gln Leu
 100 105 110

Glu Ser Phe Tyr Ile Gln Thr Leu Leu Asp Ile Val Ser Ser Tyr Gly
 115 120 125

Lys Gly Tyr val Val Trp Gln Glu Val Phe Asp Asn Lys Val Lys Ile
 130 135 140

Gln Pro Asp Thr Ile Ile Gln Val Trp Arg Glu Asp Ile Pro Val Asn
 145 150 155 160

Tyr Met Lys Glu Leu Glu Leu Val Thr Lys Ala Gly Phe Arg Ala Leu
 165 170 175

Leu Ser Ala Pro Trp Tyr Leu Asn Arg Ile Ser Tyr Gly Pro Asp Trp
 180 185 190